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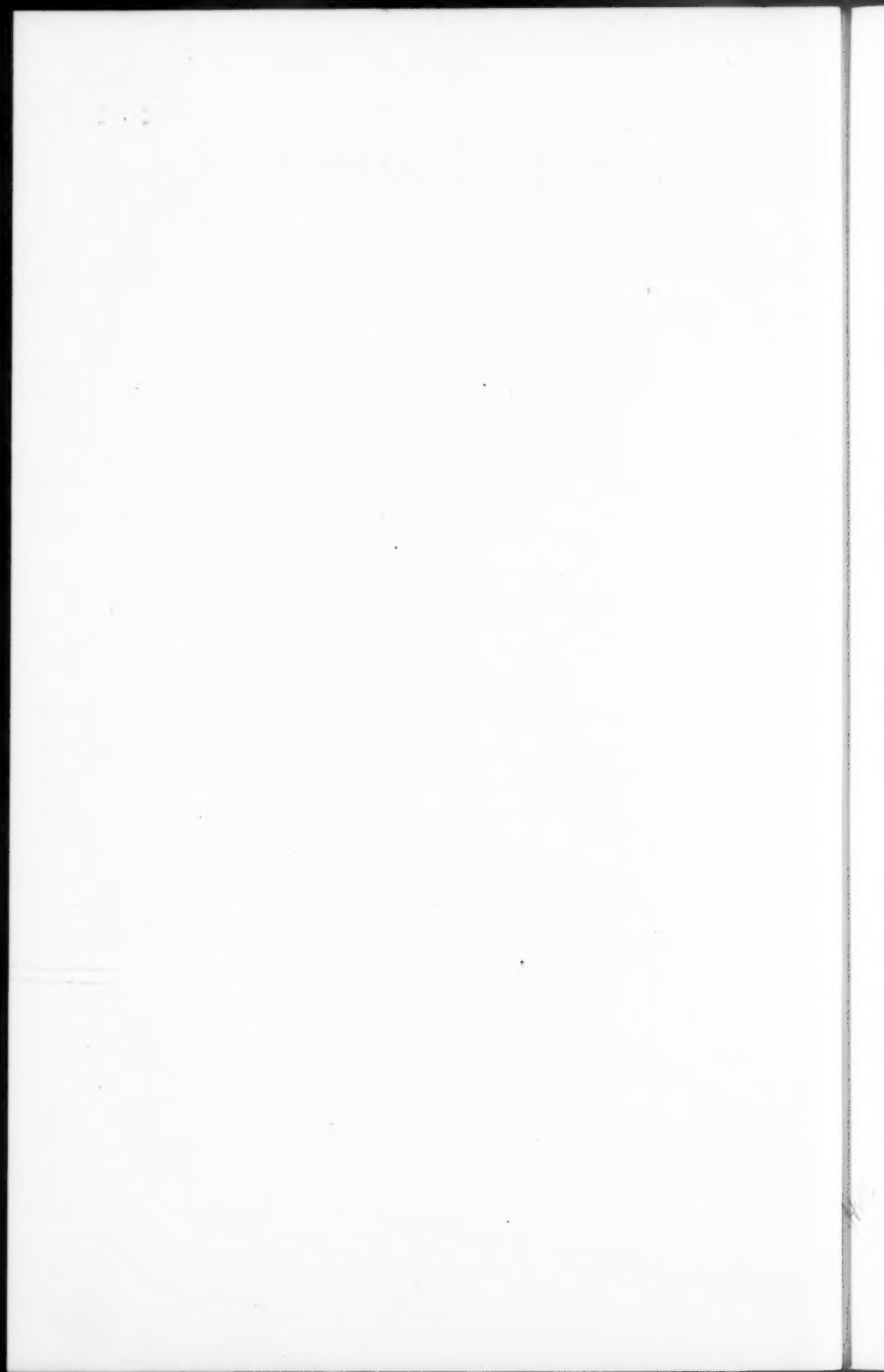
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On Congenital Pneumonia

by

E. K. AHVENAINEN

Pneumonia is one of the most important diseases of the newborn and a frequent cause of death in early life (15). The infant can contract infection ante partum, intra partum, or post partum. The purpose of this paper is to direct attention toward infection occurring before birth and to evaluate it clinically.

Literature

As early as the last century it was noted that aspiration of infected amniotic fluid could produce pneumonia (13, 7). HESS-THAYSEN (1914) (8) stated that aspiration during birth was the most common cause of pneumonia in newborn. There is no general agreement as to when pneumonia can be considered congenital. According to HOOK and KATZ (9), pneumonia dignosed at autopsy is congenital only in a stillborn or in an infant who has lived not more than two-three hours. Clinically only pneumonia producing symptoms immediately after birth can be diagnosed as congenital pneumonia. Thus the diagnosis of congenital pneumonia is difficult. It is even more difficult to prove that infection is congenital in cases where pneumonia develops later. Bacteriologic studies and inspection of the placenta can be a great help in these cases (4). Post mortem cultures of lungs have shown that congenital pneumonias are caused by staphylococci, colobacterium coli, and streptococci (8, 9, 10). Bacteriology has often given negative results. This has given rise to the hypothesis that even a sterile amniotic fluid can produce pneumonia chemically or

mechanically (10, 12, 16, 17). It is also assumed that aspirated amniotic fluid can produce a "locus minoris resistentiae" and thus be partly responsible for pneumonia (6).

Viri have likewise been incriminated as a cause of congenital pneumonia (1). No virus has been isolated, however.

In different statistics congenital pneumonia is diagnosed at autopsy in 0-50 % (14, 6, 5, 9). These statistics refer only to stillborns and newborns who have died two-three hours after birth.

Material and Methods

This material is made up only of stillborns. It is agreed that congenital pneumonias occur also in live births, but these are to be published in a different paper together with other pneumonias of newborns.

The material contains 45 cases: 13 prematures (birth weight \leq 2500 gm) and 32 full-terms (birth weight $>$ 2500 gm). All autopsies were performed by the writer. In each case blocks were taken from all lung lobes. Paraffin sections were stained with hematoxylin and eosin and hematoxylin van Gieson. Frozen sections were stained with Scharlach R. Clinical notes were taken from delivery reports. The material was collected for two years and comprises all cases obtained for autopsy. Only macerated cases were omitted. Bacteriologic studies were not undertaken. The placenta was investigated only grossly.

Results

Pneumonia was diagnosed in 14 cases — 9/32 in full-terms and 5/13 in prematures. The table gives an idea of the facts obtained from delivery reports, including cause of death and histologic findings.

Delivery was frequently of long duration and complicated. Operative intervention was often necessary. In 2 cases it was necessary to perform extraction or craniotomy of the living fetus to save the life of the mother (Cases 2 and 12). In many cases

the membranes ruptured early and in some there developed signs of intrauterine infection. It was evident, however, that pneumonia could occur even in cases where the duration of delivery was short and the membranes ruptured so late that this could not be interpreted as a factor in the etiology of pneumonia (Cases 9, 11; probably also 1, 2, and 6). There was only 1 case of death during pregnancy and so few cases of death during pregnancy in the whole material that one cannot draw any conclusions from this.

Signs of infection in the mother are based on inadequate facts obtained from delivery reports. Sometimes the only sign of infection was fever, and it was not possible to find out whether there was local inflammation or not. In part, however, there was clear-cut evidence that infection of the uterus was present — the amniotic fluid was offensive or purulent fluid was recovered from the uterus after delivery (Cases 3, 5, 8, 12). Discolored amniotic fluid is no more than a sign of fetal asphyxia, if anything, and does not permit conclusions concerning inflammation of the uterine cavity.

Death was attributed in the majority of cases to fetal asphyxia. This included cases in which the fetus died following delivery complications, since the cause of death was asphyxia in these cases as well. Asphyxia was diagnosed in cases which did not reveal any signs of trauma when the facts obtained from delivery histories showed sufficient evidence for this diagnosis. When signs of trauma were present, this was indicated as a cause of death either by itself or in conjunction with asphyxia. Pneumonia was probably the cause of death in 1 case only. Pneumonia was severe in this case, and no other death causes were found. In Case 8 asphyxia and pneumonia together were the cause of death. Pneumonia was severe enough but asphyxia was at least partially produced by the birth process.

The table shows the extent of microscopic findings. In pneumonic areas there were mainly polymorphonuclear cells and some detached alveolar lining cells. The last-mentioned cells were not given much value in the diagnosis of pneumonia. In my opinion, they are not sufficient in themselves to justify a diagnosis of pneumonia in the stillborn. Material revealed in the alveoli was interpreted as aspirated amniotic fluid only when skin cells and

Table

No.	Birth Weight Sex	Mother	Duration of Delivery	Membranes Ruptured (Before Birth)	Amniotic Fluid	Complications and Operations
1	1200 gm boy	III-para 32 yrs	5 ^h 10'	4 ^h 5'	Bloody	Ablatio placentae ante tempus.
2	1340 gm girl	II-para 23 yrs	2 ^h 10'	2 ^h	Bloody	Placenta praevia, hemorrhagia, extraction of fetus
3	1350 gm girl	IV-para 34 yrs	24 ^h 25'	more than 10 ^h	Purulent fluid from uterus	Transversal presentation, placenta praevia, endometritis, extraction of fetus
4	1580 gm boy	I-para 21 yrs	13 ^h 30'	10 ^h 30'	?	
5	2500 gm boy	I-para 35 yrs	41 ^h	abt 2 d	Offensive	Eclampsism
6	2600 gm girl	I-para 31 yrs	40 ^h	1 ^h		Frontal presentation
7	2750 gm girl	I-para 40 yrs	54 ^h	30 ^h	Discolored	Eclampsism, Forceps delivery
8	3000 gm boy	I-para 25 yrs	70 ^h	20 ^h	Cloudy, offensive	None
9	3200 gm boy	II-para 26 yrs	13 ^h 6'	10'	Discolored	None
10	3380 gm boy	I-para 34 yrs	19 ^h 50'	11 ^h 40'	Discolored	Forceps delivery
11	3400 gm girl	IV-para 34 yrs	17 ^h	5'	Discolored	None
12	3580 gm boy	III-para 32 yrs	28 ^h 40'	60 ^h	Offensive	Craniotomy
13	3850 gm boy	V-para 32 yrs	7 ^h	17 ^h	Discolored	Transversal presentation, prolapse of cord, internal version, extraction of fetus, craniotomy.
14	3900 gm boy	I-para 23 yrs	31 ^h	30 ^h	?	None

Signs of Infection in Mother (Except Amniotic Fluid)	Fetus Died	Cause of Death	Microscopic Findings in Lungs
None	Intra partum	Asphyxia	Diffuse early pneumonia and bronchiolitis. Small amounts of squamæ and skin cells. Ecchymoses.
None	Intra partum	Asphyxia	In left lower lobe focal pneumonia. Small amounts amniotic fluid.
Fits of shivering Fever 40.7 C	Intra partum	Asphyxia	Diffuse early pneumonia. Bacteria. Amniotic fluid diffuse. (Aspiration of purulent amniotic fluid?)
Fever 38.5 C	Asphyxiated Not survived	Subdural hemorrhage	Focal pneumonias in every lobe. Small amounts of amniotic fluid. Ecchymoses.
2 days after delivery fever ad 38.3 C. Pyelitis	Intra partum	Asphyxia?	Diffuse pneumonia, early. Small amounts of amniotic fluid.
None	Asphyxiated Not survived	Asphyxia	In right lower lobe focal pneumonia. Small amounts of amniotic fluid.
None	Intra partum	Asphyxia and trauma	Focal pneumonias in left upper and lower lobe. Small amounts of amniotic fluid. Ecchymoses.
Fever ad 38.0 C before delivery	Intra partum	Asphyxia, pneumonia	Severe and extensive pneumonia. Abundant amounts of amniotic fluid in bronchioles.
None	Ante partum	Pneumonia	Severe pneumonia in both lower lobes. Abundant amounts of amniotic fluid. Extensive septal hemorrhages.
2 days after delivery fever ad 38.8 C	Intra partum	Subdural hemorrhage, hemoperitoneum, asphyxia	Diffuse, severe pneumonia. Abundant amount of amniotic fluid.
After delivery fever 37.9 C.	Intra partum	Asphyxia?	Focal pneumonias in every lobe. Small amounts of amniotic fluid.
Fever 38.4 C. Intra-uterine infection	Intra partum	Craniotomy	Focal pneumonia. Abundant amounts of amniotic fluid.
None	Intra partum	Asphyxia	Focal pneumonias in every lobe. Small amounts of amniotic fluid. Ecchymoses.
None	Intra partum	Asphyxia	Diffuse early pneumonia in three lobes. Small amounts of amniotic fluid.

squamae were found. Amniotic fluid was often most scanty in pneumonic areas. There was also precipitate which was either aspirated amniotic fluid or edema fluid. Fibrin was not found. Pneumonia was histologically never old. — Small groups of mononuclear cells found in some cases were not considered as evidence of inflammation. They were either lymphatic tissue or hematopoietic foci. Hemorrhages were small and recent — agonal. Extensive septal hemorrhages found in 1 case (9) were probably produced by disturbances in the pulmonary circulation. They are met with in the stillborn also without pneumonia (3).

Comment

A finding of polymorphonuclear cells in the lungs of a stillborn is not enough evidence for a diagnosis of congenital pneumonia. It is also possible that the fetus aspirated purulent amniotic fluid and leucocytes originated from the amniotic fluid and not from the fetus. This may have happened in 1 case in this material. It is, however, possible that aspiration of purulent amniotic fluid causes pneumonia. So the end result is the same.

This material suggests that at least in the majority of cases the cause of congenital pneumonia is infection from the mother. The mechanical and chemical effect of amniotic fluid does not seem to be of high value. It is evident that amniotic fluid in itself does not produce pneumonia. Skin cells and squamae are seen even in fairly large amounts in lungs without any signs of inflammation up to the age of 1 week (2). It has never been shown that sterile amniotic fluid is able to produce pneumonia. Negative post-mortem bacteriology does not prove that the inflammation could not be produced by bacteria or viri. Probably the most common cause is aspiration of infected amniotic fluid. Hematogenous infection from the mother to the fetus is not plausible without changes in the placenta. It is not known whether viral infections can proceed from the mother to the fetus without signs of inflammation in the placenta and produce pneumonia. This, as well as some other questions in congenital pneumonia, needs further study.

One possible explanation of congenital pneumonias without any signs of infection in the mother is that there are bacteria which are pathogen to the fetus without being so to the mother. Sometimes signs of infection in the mother do not become noticeable before the day following delivery, while the fetus has severe pneumonia (Case 10).

For a clinician-pediatrician it is important to know that pneumonia in an infant may originate even before birth. In some of these cases pneumonia was slight and probably produced no symptoms until some time after birth. Although the delivery was difficult in most of these cases, it is quite possible that an equally severe aspiration and infection may also occur when the baby survives. It seems clear that the newborn gets pneumonia more often in complicated deliveries than in normal ones. But even babies born by abnormal delivery are very often admitted to the Children's Hospital. It is therefore possible that in babies taken to hospital immediately after birth the pneumonia incidence is about similar to that of the stillborn in this material. The pediatrician does not always get enough facts about labor and infections in the mother or he does not pay attention to them. Therefore he does not consider the possibility of congenital infection in the newborn. This should be taken into consideration when a newborn is transferred to a non-inflammatory ward. He can be "dangerous" to his neighbours even when he is taken directly from the delivery room to the Children's Hospital.

This material does not allow too many conclusions, but one can say that in prolonged labor and when membranes rupture several hours before birth, the possibility of pneumonia of the newborn is present. When there are signs of infection in the mother and especially when inflammation of the genital passages is present, this possibility is even stronger. However, congenital pneumonia can also develop in cases where delivery is of relatively short duration and the membranes rupture shortly before birth. As a cause of fetal death pneumonia is rare.

The prophylaxis and treatment of fetal infection is in the hands of obstetricians. It is necessary to avoid prolonged labor. Antibiotic drugs can be used in the hope that they will have an

effect on the fetus as well. These questions are discussed in an recently published extensive paper about perinatal mortality (11). — When pneumonia is assumed in a newborn, it is wise to use antibiotic drugs even without a certain diagnosis of pneumonia. The only symptom of pneumonia in the newborn can be asphyxia — and even that can be lacking.

Summary

Pneumonia was found microscopically in stillborns in 14 of 45 cases. There was no difference between full-terms and prematures.

Prolonged delivery, infections of the mother, and early ruptures of membranes are often seen in pneumonia cases, but pneumonia can develop even in cases without any complications during labor.

As a cause of fetal death pneumonia is rare. According to this material, in the etiology of pneumonia of the newborn congenital pneumonia is an important factor to be taken into account. This knowledge is also of importance to the clinician.

E. K. AHVENAINEN: *Pneumonie congénitale.*

On a trouvé microscopiquement signes d'inflammation pulmonaire chez les nouveaux nés dans 14 cas sur 45. Il n'y avait aucune différence entre les nouveaux nés à terme et les prématurés.

Un accouchement prolongé, des infections de la mère et la rupture précoce des membranes sont souvent observés dans les cas de pneumonie, mais la pneumonie peut se développer même dans les cas sans aucunes complications pendant le travail.

Comme causes de mort foetale, la pneumonie est rare. Selon ce matériel, dans l'étiologie de la pneumonie du nouveau né, la pneumonie congénitale est un important facteur dont on doit tenir compte. Sa connaissance est aussi importante pour le clinicien.

E. K. AHVENAINEN: *Kongenitale Pneumonie.*

In mikroskopischen Untersuchungen wurde in 14 Fällen unter 45 Totgeburten Pneumonie gefunden. Dabei war kein Unterschied festzustellen zwischen ausgetragenen Kindern und Frühgeburten.

Verlängerte Geburtsdauer, Infektionen der Mutter und früher Blasensprung war oft nachzuweisen in den Pneumonie-Fällen. Aber eine Pneumonie kann sich auch entwickeln ohne irgendwelche Komplikationen während der Geburt.

Als Ursache von Fruchttod kommt die Pneumonie selten in Betracht. Auf Grund dieses Materials ist die congenitale Pneumonie in der Ätiologie der Neugeborenen-Pneumonie ein wichtiger Faktor, mit dem man zu rechnen hat. Diese Erkenntnis ist auch für den Kliniker von Bedeutung.

E. K. AHVENAINEN: *Neumonia congenital.*

De 45 niños nacidos muertos se presentan 14 casos en los cuales se ha demostrado la neumonía en examen microscópico. No se ha notado diferencia alguna entre los nacidos a término y los prematuros.

El parto prolongado, infecciones en la madre y la rotura prematura de membranas se han asociado con los casos de neumonía, pero la neumonía puede desarrollarse también cuando no existen complicaciones durante el parto.

La neumonía causa raramente mortalidad fetal. El material presentado indica que la neumonía congénita puede desempeñar un papel importante en la génesis de la neumonía en el recién nacido. Esta observación es también de importancia para el médico.

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Anoxia in Infantile Dehydration

by

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In an earlier paper (1) the analysis of 42 dehydrated "toxic" infants revealed that "toxic" symptoms begin to appear at an approximately trebled circulation time. Slowing of circulation of such an extent implies that the blood supply to the tissues is diminished in a unit of time. Cardiac output decreases roughly parallel with the slowing of circulation. The most prominent features of infantile "toxicosis", appearing in the course of progressing dehydration, are secondary consequences of decrease in cardiac output: The characteristic *neurologic symptoms* were found to be correlated with the extent of cerebral anoxia, as measured by the decrease in O_2 saturation of the cerebral venous blood (2). *Acidosis*, chiefly caused by the increase of organic acids (3, 4, 5), was found to be a direct consequence of anoxia and deterioration of *kidney function*. The latter can be correlated, as shown by VAN SLYKE and others (6, 1) to decrease in cardiac output.

Thus, the "anhydremic theory" of infantile toxicosis of MARRIOTT (7) and UTHEIM (8) was put on a more quantitative basis.

In this work, the origin, extent and prevention of anoxia, arising in infantile dehydration, will be studied.

Extent and origin of anoxia can best be estimated from the balance of O_2 transported to the tissues and O_2 consumption.

In endeavouring to do this, we measured, in 5 normal and 10 dehydrated infants, (a) O_2 consumption, (b) the amount of O_2 transported to the tissues in a unit of time (i.e., cardiac output \times Vol. % of arterial O_2). (c) The obtained data were compared with the arterio-venous O_2 difference found in each case.

I. Methods

The infants observed in this study were dehydrated following "aspecific" or "parenteral" vomiting and diarrhea. There was no case beginning with acute cerebral symptoms as found in "toxic" dysentery or in cases of encephalitis. "Toxic" symptoms always appeared clearly in the course of progressing dehydration. The intensity of the former varied from milder signs to the fully developed picture, as described by FINKELSTEIN (9). The O_2 in the blood was determined according to VAN SLYKE (10). The O_2 consumption was measured in KESTNER's (11) close circuit apparatus in experiments of one hour's duration. Food was withheld from normal infants for 6—8 hours; water however was given. According to the procedure of SCHADOW, 5—10 drops of somnifen were administered by mouth prior to the experiment to exclude restlessness. This procedure was found to be unnecessary in most cases of "toxicosis".—The latter cases were put into the respirator immediately after admission to the clinic.

Our method used to measure " O_2 transport" is open to some criticism. To calculate the former, we have to measure first the minute volume of the heart. This is classically determined by the FICK principle (12). The output is calculated from the arterio-venous O_2 difference and the total O_2 consumption.

$$\text{Cardiac output} = \frac{\text{total } O_2 \text{ consumption}}{\text{Vol. \% arterial } O_2 - \text{Vol. \% venous } O_2}$$

The O_2 content of the arterial blood is the same in the whole arterial system, and therefore, the puncture of any artery will supply adequate information. The difficulty of applying the Fick principle to infants lies obviously in obtaining the O_2 content of mixed venous blood. To obtain the latter, catheterisation of the right heart has to be performed, as the O_2 content of venous blood of each tissue varies according to its own O_2 consumption. Catheterisation of the right heart in a series of "toxic" infants presents, however, obvious difficulties and dangers. Apprehension of the infant may also lead to erroneously low venous O_2 values. We have chosen to use in our calculation the O_2 content of cerebral venous

blood by puncturing the sinus longitudinalis. We felt this permissible on the basis of following considerations:

(1) The O_2 content of cerebral venous blood is, in normal cases, remarkably constant (13, 2). (2) In the case of two normal and two dehydrated infants we measured simultaneously the O_2 content of mixed and cerebral venous blood, and found, as shown in table I, that cardiac output in normal infants is only some 10 % lower when calculated from cerebral venous blood instead from mixed venous blood.

On the other hand, pathological changes in dehydration were found to be of such an extent, that relatively small differences in calculating cardiac output seem to be irrelevant.

Table I.

	O_2 arter. blood	O_2 sinus	O_2 right heart	Total O_2 con- sumption	Cardiac output from art. - sinus O_2	Cardiac output from art. - right heart O_2
Normal I	12.0	5.2	5.8	220	3 230	3 550
Normal II	11.0	4.2	4.4	240	3 580	3 810
Dehydration I	19	8.9	5.4	180	1 800	1 323
Dehydration II	14.5	5.4	5.9	200	2 197	2 279

(3) Cardiac output can also be roughly estimated from circulation time and blood volume (14, 15, 16). Both were determined in all of our cases, and cardiac outputs obtained by both methods agreed reasonably well in all cases of dehydration. It will be pointed out however, on another occasion, that there are cases of so called "hyperventilation toxicosis" (17, 18, 19) and some other clinical pictures (20) where cerebral circulation or O_2 metabolism varies independently of the general circulation. This however was never the case, as mentioned before, in dehydration "toxicosis".

II. Experimental Data

Figure I shows data on O_2 metabolism in dehydration. All values are related, according to Rubner's law, to surface area. The latter was calculated from the tables of Du Bois. Instead of

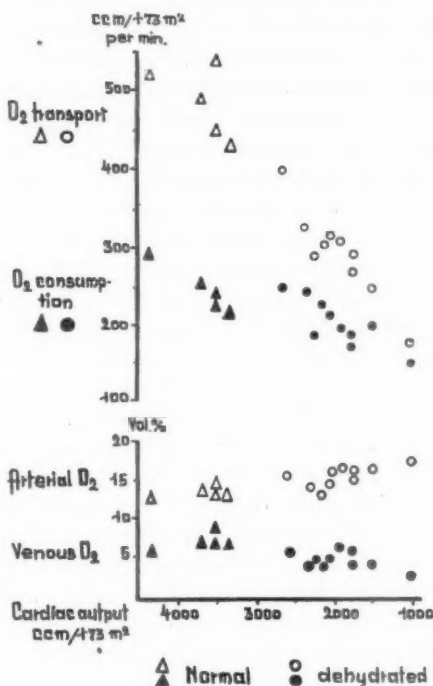


Fig. I.

1 sq. m of surface area, we preferred to use, as done in studies on renal function in early life (21), the surface area of 1.73 sq. m of the adult. This permits comparison with conditions existing in the adult.

The severity of the "toxic" condition in dehydration can be related, as shown in an earlier paper (1) to cardiac output. Thus, the latter is used in our figure as abscissa. Accordingly we proceed, reading the figure from left to right, from normal cases to cases of increasing severity.

The cardiac output of *normal infants* ranges between 4 300—3 300 ccm. ("True values" may be, as described above, some 10 % higher.) Cardiac output decreased in the severest cases of dehydration to 1/4 of the normal value.

The lower ordinate shows the O_2 content of venous (\blacktriangle) and arterial (\triangle) blood. The latter is, because of the physiologically low hemoglobin content of the infant, always lower than the standard value (19—20 Vol.%) of the healthy adult. Our values range between 12—15 Vol.%.—In toxic cases, hemoglobin, and consequently O_2 content of the arterial blood, increase, the oxygenisation in the lungs being generally normal.

The O_2 content of the venous blood moves in the opposite direction. Therefore, the more severe the case, an ever increasing broadening of the arterio-venous O_2 difference results. The latter process indicates that each cc of blood gives up an increasingly larger proportion of its O_2 load to the tissues than in normal infants. *The O_2 supplied to the tissues is, in spite of higher O_2 utilisation per cc of blood, increasingly smaller, because at the same time cardiac output, and thus, O_2 transport to the tissues decreases.*

This can be read from the upper ordinate scale, showing changes in O_2 transport (cardiac output \times Vol.% arterial O_2) in cases of dehydration of ever increasing severity. In the normal infant, O_2 transport is more than double the O_2 consumption. In dehydration, however, the amount of O_2 transported to the tissues decreases progressively. There results, as seen from the figure, a *dangerous, and ever progressing narrowing between O_2 supply and consumption*. In the earlier stages of dehydration O_2 consumption may reach even high normal values; there are some cases with temperatures reaching 38°C . The normal consumption is achieved, however, at the cost of increased O_2 utilisation of each cc of blood, as indicated by the broadening of the arterio-venous O_2 differences. This implies that towards the venous end of the capillaries O_2 saturation, and therefore O_2 pressure, decreases far more than normally. As O_2 uptake depends of O_2 pressure, it can be concluded, that in the tissues supplied by the distal end of the capillaries, anoxia may exist even if total O_2 consumption is still appearing normal. Finally, in the severest cases, total O_2 consumption also decreases as a result of the low amounts of O_2 available for metabolic needs.

In the severest cases, decrease in cardiac output is of such an

extent, that O_2 transport is almost as small as O_2 consumption. Almost all the O_2 supplied is used up; even so, O_2 consumption is significantly lowered. O_2 transport in these severe cases is even lower, than O_2 consumption in normals.

Decreased O_2 consumption may result from three causes: (1) The metabolic need of the tissues may primarily diminish. That is the case in hypothyroidism and in certain cases of infantile atrophy (22). (2) In the "histotoxic" type of anoxia, and in the "serous inflammation" type of Eppinger, cells of normal metabolic need cannot take up the O_2 offered to them. (3) The metabolic need is normal or even high, but the extent of O_2 transport is insufficient to meet demands. Figure I clearly indicates that in dehydration we deal with the latter condition: The values of O_2 transport and consumption are dangerously near to each other, the arterio-venous difference is broadened. Thus, *dehydration can be defined as a condition of anoxia of the stagnating type: Tissues of normal or even high metabolic need are inadequately supplied with O_2 . The underlying cause of this is diminution in cardiac output.*

Figure II shows that the *severity of hemodynamic insufficiency and anoxia in infantile toxicosis corresponds closely to conditions found in traumatic shock.* We want to emphasize, that there is a striking similarity in the clinical picture of both conditions: Cold extremities, low blood pressure, acidosis, changed type of breathing, azotaemia, finally nervous depression bordering on coma, are the most striking common clinical features in both pictures. All these events are induced in dehydration, as well as in traumatic shock, by decrease in blood volume and cardiac output.

The height of each column indicates the percent increase or decrease of hemodynamic values compared with normal standards. The normal value is indicated by the horizontal line (100 %). Data on traumatic shock are recalculated from GREGERSEN's (23) figures in dogs (blackened columns). The white columns represent figures from the most severely "toxic" case of the present series of dehydrated infants.

It can be stated that plasma volume, stroke volume, cardiac output and O_2 consumption decrease almost parallel with both

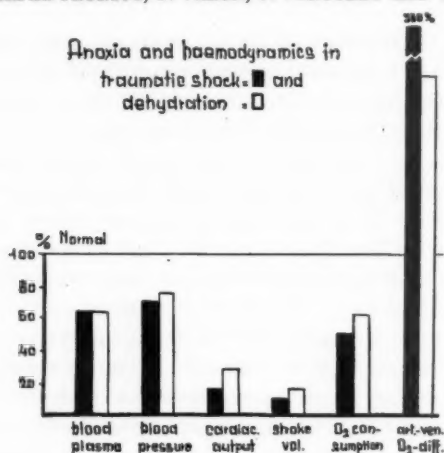


Fig. II.

conditions to remarkably low values. Only the arterio-venous O₂ difference is somewhat broader in dogs than in infants, presumably on account of the lower hemoglobin and O₂ content of the latter.

We feel that this comparison between hemodynamic data in traumatic shock and "toxicosis" supports the belief that the latter picture originates in an anhydremic, anoxic circulatory disturbance.

CO₂ metabolism showed parallel changes to that of O₂. Arterio-venous CO₂ difference increased considerably.

R.Q. shows a tendency to low values. In figure III we have plotted R.Q. against circulation time.

It can be seen that the circulation time is much prolonged in all our cases. That corresponds to a decrease in cardiac output, as described in figure I. R.Q. is lower than in our fasting normal infants. A close correlation between circulatory failure and decrease in R.Q. could not be stated. We feel, however, that low values, surpassing the usually fasting levels, are indicative of incomplete oxydative processes. This is suggested also by other metabolic abnormalities, i.e., accumulation of organic acids (3, 4, 5) and increased carbon/nitrogen ratio of the urine (8).

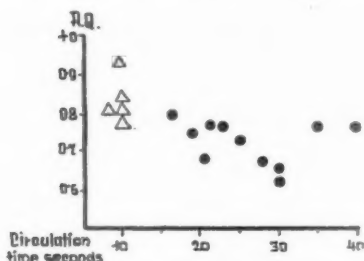


Fig. III.

In conclusion some factors will be discussed that may aggravate anoxia in dehydration.

It is obvious that every factor capable of increasing the call of the tissues for O_2 without increasing simultaneously cardiac output, will aggravate anoxia. Such factors are fever, restlessness of the patient and a diet rich in proteins.

In fig. IV the influence of high fever on O_2 metabolism is demonstrated in a dehydrated compared with a normally hydrated infant.

The construction of the figure is the same as in fig. I. It can be seen, that the cardiac output of the "normal" infant is highly increased by fever. It rose to 5 250 cc, compared with the normal average value of 3 500 cc. Therefore, the higher demand of the cells for O_2 can be met by an increased transport of O_2 to the tissues (upper line). The increased demand is nicely balanced by an increased supply; the arterio-venous O_2 difference remains unchanged. There is no anoxia.

In the dehydrated infant cardiac output is fixed by anhydraemia to a low level. The former cannot be adjusted to the increased call of the tissues for O_2 induced by fever. Therefore, there results a dangerous disparity between O_2 consumption, and delivery of O_2 to the tissues. The arterio-venous O_2 difference is trebled. The infant presented the picture of the fully developed toxicosis, although the actual reduction of his cardiac output, to 2 200 ccm., would still have permitted,—without fever—a more or less satisfactory O_2 metabolism.

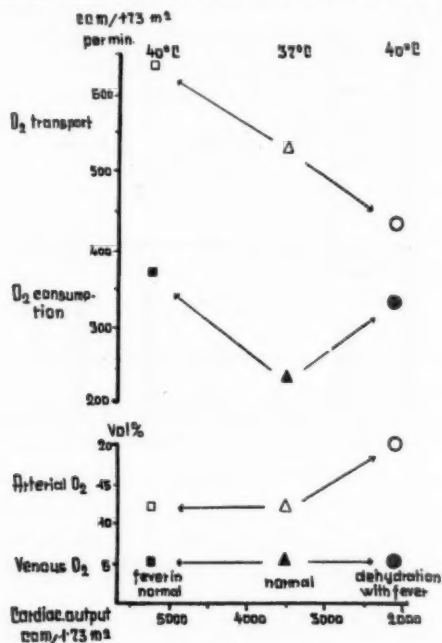


Fig. IV.

In this connection we have to go back to fig. I. None of the dehydrated infants of this series had higher temperatures than 38° C. In the severest cases we found a low O₂ consumption. It should be pointed out, however, as seen from fig. III that *lowering of O₂ consumption is not in itself the criterium of oxygen want*. The latter can exist even in the case of a high O₂ consumption in every case, when the actual and total need of the tissues is not covered by adequate circulation. Broadening of the arterio-venous O₂ difference and consequent lowering of venous O₂ saturation reveal such conditions. Venous O₂ saturation fell in the case described in fig. III to 20 %, although O₂ consumption was high, and cardiac output (compared to "normal output" without fever) was reduced only by 30 %. To prevent anoxia, the latter should have been, however, increased by the fever to the high level reached

by the well hydrated feverish infant. *Fever will therefore induce anoxia at earlier stages of dehydration than in cases without fever.* In the latter, cardiac output must fall to far lower values to cause anoxia; anoxia will, in such cases, be certainly accompanied by lowered total O_2 consumption, as shown in fig. I.

Restlessness of the dehydrated patient induces anoxia much in the same way as fever. O_2 consumption in normal infants may increase, by muscular movements and crying, up to 100 % (24, 25). In the case of the cardiac output fixed at a low figure by dehydration, anoxia, i.e., disparity between O_2 demand and supply will arise at early stages of dehydration.

The same holds true when *diets rich in protein* are fed. The specific dynamic action of protein increases the call of the tissues for O_2 , this can be only inadequately met in case of circulatory failure. It should be remembered, that carbohydrates do not exert any specific dynamic action.

The heaviest burden to O_2 metabolism in dehydration is *intercurrent pneumonia*. The arterial O_2 load is seriously diminished by pneumonic processes (26, 27, 2). Cardiac output is decreased by dehydration. On the other hand, O_2 demand is increased by fever and infection. The net result is anoxia of the severest degree. The described peculiarities of O_2 metabolism in pneumonia, complicating dehydration, explain the high case fatality (28) of this complication.

The treatment of anoxia in dehydration should aim at the correction of the disparity between O_2 supply and demand. First, cardiac output has to be raised by correcting anhydremic circulatory failure. Second, O_2 should be supplied in case of respiratory infection to increase the O_2 load of the blood. Third, we want to emphasize, that O_2 consumption, i.e., demand, has to be brought down to basal levels. Fever, infection, restlessness has to be treated, proteins are to be avoided.

Treatment has to be quick and effective because of the danger of irreversibility of shock and possible anoxic damage to the brain.

Summary

The balance between O_2 transported to the tissues and O_2 consumption was studied in 10 dehydrated and 5 normal infants. The obtained data were compared to the arterio-venous O_2 difference found in each case.

The amount of O_2 supplied to the tissues (cardiac output \times Vol. % of arterial O_2) was found to decrease parallel with increasing dehydration. The decrease in O_2 supply is caused by an enormous fall in cardiac output. The ever progressing narrowing between O_2 demand and supply results in a condition of anoxia of the stagnating type comparable in its extent with conditions described in traumatic shock.

Anoxia in dehydration is aggravated by every factor capable of increasing the call of tissues for O_2 , because dehydration, i.e., anhydremia, prevents adjustment of circulation to higher metabolic needs. Thus, fever, restlessness of the patient, a diet rich in proteins may induce anoxia at relatively mild stages of dehydration. The most dangerous complication of dehydration is pneumonia. There is a simultaneous lowering of the arterial O_2 load and a decreased cardiac output. On the other hand, O_2 demand is increased by fever. In severely dehydrated cases, without fever, O_2 consumption decreases significantly.

The treatment of anoxia in dehydration should aim at the correction of disparity between O_2 supply and demand. Cardiac output is raised by correcting anhydremic circulatory failure. At the same time O_2 demand of the tissues has to be brought down to basal levels by treating fever, infection, restlessness and avoiding proteins.

E. KERPEL-FRONIUS, F. VARGA, J. VÖNÖCZKY et K. KUN: *L'anoxie dans la déshydratation infantile.*

Le rapport du taux d' O_2 apporté aux tissus et celui de la consommation en O_2 a été étudié au cours de 10 cas de syndrome de déshydratation et chez 5 enfants normaux. Les chiffres obtenus furent comparés au rapport O_2 artériel et O_2 veineux trouvés dans chaque cas.

Il fut trouvé que la quantité d'oxygène délivrée aux tissus (débit cardiaque \times vol. % d' O_2 artériel) décroît à mesure qu'augmente la déshydratation. La décroissance de l'apport en O_2 est due à une très importante diminution du débit cardiaque. Le rapprochement progressif du besoin et de l'apport en O_2 provoque une anoxie comparable quant à son étendue aux conditions existant au cours du choc traumatique.

L'anoxie au cours de la déshydratation est aggravée par tous les facteurs susceptibles d'augmenter les besoins en O_2 des tissus, car la déshydratation, en d'autres termes l'anhydrémie, empêche l'adaptation de la circulation sanguine à des besoins métaboliques supplémentaires. Ainsi, la fièvre, le manque de repos, un régime riche en protéines peuvent

provoquer une anoxie au cours d'un syndrome de déshydratation relativement peu avancé. C'est la pneumonie qui constitue la complication la plus dangereuse de la déshydratation. Il existe simultanément une diminution de charge en O_2 artériel et un abaissement du débit cardiaque. Cependant, la demande en O_2 est augmentée par la fièvre. Dans les cas de déshydratation sévère, sans fièvre, la consommation en O_2 est nettement inférieure.

Le traitement de l'anoxie au cours de la déshydratation doit tendre à corriger le déséquilibre du rapport besoin-consommation en O_2 . Le débit cardiaque sera augmenté par une correction de la déficience circulatoire. En même temps la demande en O_2 des tissus devra être abaissée au maximum par une thérapeutique antithermique, anti-infectieuse, le repos et un régime pauvre en protéines.

E. KERPEL-FRONIUS, F. VARGA, J. VÖNÖCZKY und K. KUN:
Anoxie bei dehydrierten Säuglingen.

Das Gleichgewicht zwischen O_2 , der zu den Geweben transportiert wurde, und dem O_2 -Verbrauch wurde untersucht bei 10 dehydrierten und 5 normalen Säuglingen. Die erhaltenen Werte wurden verglichen mit den arterio-venösen O_2 -Differenzen, die in jedem Falle ermittelt wurden.

Die O_2 -Menge, mit denen die Gewebe versorgt wurden (Schlagvolumen \times Volumen% des arteriellen O_2), nahm ab parallel zur zunehmenden Dehydration. Die Abnahme der O_2 -Versorgung wird verursacht durch beträchtlichen Abfall des Schlagvolumens. Die stetig zunehmende Annäherung zwischen O_2 -Bedarf und Versorgung führt zu einem Zustand von Anoxie vom stagnierenden Typ, vergleichbar im Ausmass mit Zuständen im traumatischem Shock.

Die Anoxie bei Dehydration ist verschlimmert durch jeden Faktor, der das Verlangen der Gewebe nach O_2 vermehren kann, weil Dehydration, d. h. Anhydraemie, die Anpassung der Zirkulation an höheren Stoffwechselbedarf verhindert. So können Fieber, Unruhe des Patienten, eiweissreiche Diät Anoxie verursachen bei verhältnismässig geringem Ausmass der Dehydration. Die gefährlichste Komplikation der Dehydration ist die Pneumonie. Dabei besteht eine gleichzeitige Verringerung des arteriellen O_2 -Gehaltes und verringertes Schlagvolumen. Andererseits ist der O_2 -Bedarf bei Fieber vermehrt. In schwer dehydrierten Fällen, ohne Fieber, sinkt der O_2 -Verbrauch beträchtlich.

Die Anoxie-Behandlung bei Dehydration sollte eine Verbesserung der Ungleichheit zwischen O_2 -Versorgung und -Bedarf anstreben. Das Herzvolumen wird vermehrt durch Korrektur der anhydraemischen Kreislaufstörung. Gleichzeitig muss der O_2 -Bedarf der Gewebe herun-tergesetzt werden durch Behandlung des Fiebers, der Infektion, Unruhe und durch Vermeidung von Proteinen.

E. KERPEL-FRONIUS, F. VARGA, J. VÖNÖCZKY, y K. KUN: *Anoxia en deshidratación infantil.*

El equilibrio entre el O_2 transportado al organismo y el O_2 consumido se ha estudiado en 10 niños deshidratados y 5 normales. Los datos obtenidos fueron comparados a la diferencia de O_2 arteriovenoso en cada caso.

Se vió que la cantidad de O_2 suministrado al organismo (eliminación cardíaca \times Vol. % de O_2 arterial) disminuía paralelamente al aumento de deshidratación. La disminución del suministro de O_2 se debe a la enorme rebaja de la eliminación cardíaca. El estrechamiento progresivo entre la demanda y el suministro de O_2 resulta en una condición de anoxia del tipo de estancamiento comparable en su severidad con las condiciones descritas en "shock" traumático.

La anoxia en deshidratación se agrava por todo factor capaz de aumentar la demanda de O_2 por el organismo, porque la deshidratación, es decir anhidremia, no permite ajustar la circulación a necesidades metabólicas más elevadas. Así que la fiebre, el desasosiego del paciente, o una dieta rica en proteínas pueden causar la anoxia en estados de deshidratación relativamente leves. La complicación más peligrosa de la deshidratación es la pulmonía. La disminución del O_2 arterial ocurre simultáneamente con la rebaja de la eliminación cardíaca. En casos severamente deshidratados, sin fiebre, el consumo de O_2 disminuye significativamente.

El tratamiento de anoxia en la deshidratación debe tender a corregir la desigualdad entre la demanda y el suministro de O_2 . La eliminación cardíaca se eleva corrigiendo la disminución causada por anhidremia en la circulación. A la se vez debe disminuir la demanda de O_2 del organismo a niveles básicos, tratando la fiebre, infección e inquietud, y evitando las proteínas.

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FROM THE PEDIATRIC DEPARTMENT OF THE SUNDBY HOSPITAL, COPENHAGEN. CHIEF PHYSICIAN: C. FRIDERICHSEN, M.D.

Acute Infectious Atelectasis Simulating Bronchopneumonia in Infants

Symptomatology and Treatment

by

TORBEN JERSILD and NIELS RISKÆR

The death rate from pneumonia in children under the age of 1 year is surprisingly high in this country, so that every effort should be made to reduce it.

Recently this problem has been discussed in several papers in connection with Friderichsen's "single massive dose therapy" with sulfathiazole. FRIDERICHSEN and WALTHER (1949) and BUCH (1949) reported a death rate of about 13 % for children under 1 year, while HEINTZELMANN (1942) found a mortality of 17 %. The cause of the difference between the high mortality of pneumonia in infants (in spite of sulfa and penicillin therapy) and the very low mortality of the disease in older children does not appear to have been explained satisfactorily. Serious congenital malformations may play some part in the higher mortality of the youngest infants, but in the majority of fatal cases there seems to be no other explanation except the too late institution of treatment or under-dosage of the drug employed prior to admission to hospital. On going through the autopsy records of the Pediatric Department of the Sundby Hospital, it was striking that the rather frequent demonstration of atelectasis post-mortem had not been suspected clinically. Nor has sufficient attention been paid to this aspect of the problem by other authors. For instance, BUCH (1949) mentioned atelectasis as an autopsy diagnosis in 6 children (5 of them under 1 year) out of a total of 43 children who died under the diagnosis of pneumonia.

The main reason, no doubt, that the morbid condition which, in the Sundby Hospital, we have called "acute infectious atelectasis" has not yet been established clinically is because X-ray examination is often not considered justifiable in these markedly exhausted children, who have to be kept at rest as much as possible and treated only with oxygen and chemotherapy. For this reason, the chance of recognizing correctly the true nature of the lesion is lost.

As an illustration of the clinical picture of *acute infectious atelectasis in infants* it would be appropriate to summarize here two characteristic case histories of children admitted to this department in one month, both under the diagnosis of pneumonia—one of them almost moribund at the time of admission:

Case 1. (No. 107/50). Girl, 3 months old. Admitted 3.2. 1950 and discharged on 20.3. 1950.

The child was born 2—3 months before term. Birth weight 1900 g; weight on admission, 3300 g. Bottle-fed. One week before admission: restlessness, dyspnea, vomiting, and a few thin stools.

Physical exam.: On admission, the child is markedly exhausted, greyish, breathing very rapidly (respiratory rate 70/min.). Dilatation of the nostrils and pronounced inspiratory retraction of the suprasternal notch and epigastrium, but no stridor. *Auscultation of the lungs:* semi-moist, subcrepitant râles heard over the right anterior and posterior surfaces. Temperature 36.8°.

Treatment: Sulfathiazole and oxygen.

During the following 12 hours the condition of the child got worse and in spite of the oxygen therapy the child was restless and extremely dyspneic with inspiratory retractions, protruding chest wall and shallow breathing, accompanied by jerky movements of the head synchronous with the respiration. There were frequent attacks of severe coughing; and as soon as the child was taken out of the oxygen tent, cyanosis appeared. Temp. 37.7°.

As atelectasis was suspected, an X-ray picture was taken of the child in the ward with a portable X-ray apparatus. It showed atelectasis of the right upper lobe (Fig. 1 a). On the day after admission, *bronchoscopy* was performed with the Negus baby bronchoscope (by Dr. RISKÆR). A very abundant tenacious greenish-yellow secretion was found in the trachea and both main bronchi, especially in the right. The mucous membrane was swollen, again especially on the right side, where the lumen was distinctly narrowed. The secretion was aspirated (cultures

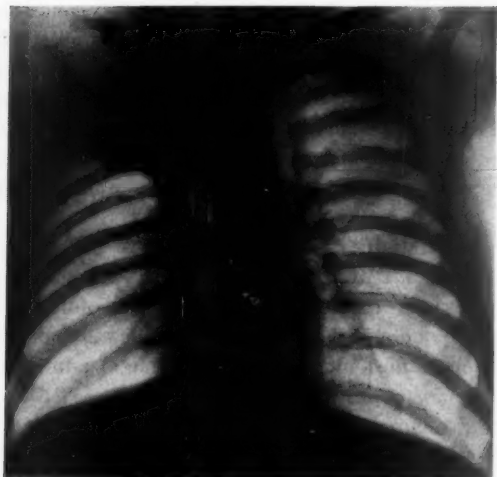
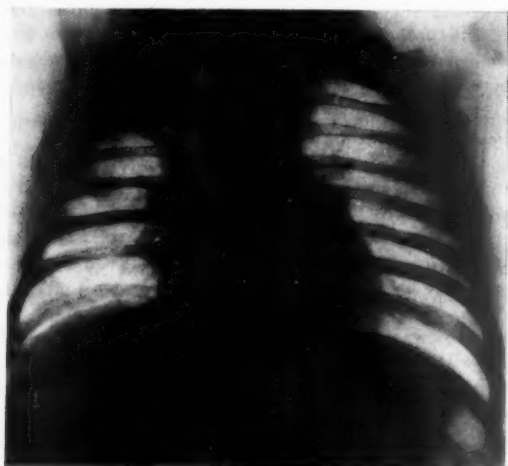
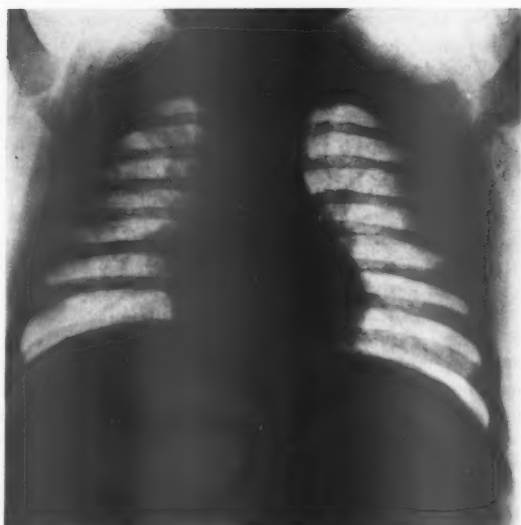


Fig. 1. Case 1. Girl, 3 months old.

a: Atelectasis of the right upper lobe (February 4).



b: 3 days after bronchoscopy with aspiration. Atelectasis almost subsided (February 7).



c. Atelectasis all gone (February 11).

gave growth of pneumococcus type 33 and *B. coli*), and oxygen was administered. After this, the respiration improved considerably.

Treatment with penicillin was now instituted, 60 000 I.U. 3 times daily.

8 hours later the condition of the child again deteriorated, and death seemed imminent. The respiratory rate was about 100/min. in spite of stimulation with lobeline and oxedrin.

On the following day, February 5, *bronchoscopy* was repeated, with aspiration of a considerable amount of tenacious secretion, though distinctly less than before. On introduction of the bronchoscope, which was easy enough, the respiration stopped, but was soon re-established by administration of oxygen through the bronchoscope. Treatment was now supplemented with streptomycin, 100 mg twice daily intramuscularly and penicillin and streptomycin inhalations.

For the next 2 days the condition of the child improved strikingly. Even on the day after the second bronchoscopy (February 6) no cyanosis appeared when the oxygen was stopped, and the respiration rate was almost normal 24 hours later without retraction of the suprasternal notch and epigastrium. The child cried lustily.

The roentgenographic findings are reproduced in Fig. 1.

On discharge, the child was perfectly well.

Case 2 (No. 182/50). Girl, 2 months old, breast-fed. Admitted 4.3. 1950 and discharged on 15.3. 50.

The child was born at term by spontaneous delivery. Birth weight: 4 000 g. Weight on admission: 5 100 g.

Previously well. 4 days before admission, coryza with cough. The temperature did not exceed 37.5°. On the day before admission the child was distinctly dyspneic, crying and restless. She was treated at home with steam and sulfathiazole—without any improvement.

Physical exam.: On admission the child was lively and not particularly distressed. Respiratory rate: 40/min., with distinct inspiratory retraction of the epigastrium. *Auscultation of the lungs*: Breath sounds weak over the right posterior surface, and a few subcrepitant râles. Temperature 37.2°. Clinical diagnosis: Bronchopneumonia.

Treatment: Steam and oxygen.

The following morning (March 5) there was an obvious deterioration in the condition of the child. She was greyish and slightly cyanotic, more dyspneic, with distended nostrils and, in spite of the oxygen therapy, had increasingly marked retractions of the epigastrium and suprasternally together with shallow breathing (respiratory rate 80/min.). No stridor, but tenacious greyish secretion in the mouth. Temperature 37.5°. *Auscultation of the lungs*: Dullness and impairment of respiration and crepitant râles over the upper part of the right anterior and posterior surfaces. *X-ray examination* of the lungs (performed in the ward) showed atelectasis of the right superior lobe (Fig. 2 a). *Bronchoscopy* was then performed with the Negus baby bronchoscope. In the trachea and right main bronchus, there was abundant greyish, foamy but not particularly tenacious secretion with marked swelling of the mucous membrane. On aspiration, fresh amounts of secretion appeared continuously into the bronchus, so that 10—12 cc in all was aspirated. The secretion itself was slightly lumpy reminding one of oatmeal gruel (Fig. 3). The bronchoscopy was tolerated well. Cultures from the aspirated secretion yielded growth of gram-positive cocci (staphylococcus aureus and enterococci) and gram-negative rods. After the bronchoscopy, treatment was commenced with dihydrostreptomycin, 50 mg 4 times daily, procaine penicillin, 250 000 I.U., and penicillin and streptomycin inhalation.

5 hours later the bronchoscopy was repeated, and 3—4 cc of very tenacious secretion was aspirated from the right main bronchus.

After this, the condition of the child improved considerably, and the respiratory rate fell from 80 to 52 per min. Distinct respiratory retractions persisted, however, although the breathing was less laborious and not as jerky as prior to the aspiration. The colour of the skin was good, and the child cried lustily.

3 hours later bronchoscopy was carried out for a third time but there was only a scanty amount of secretion present.

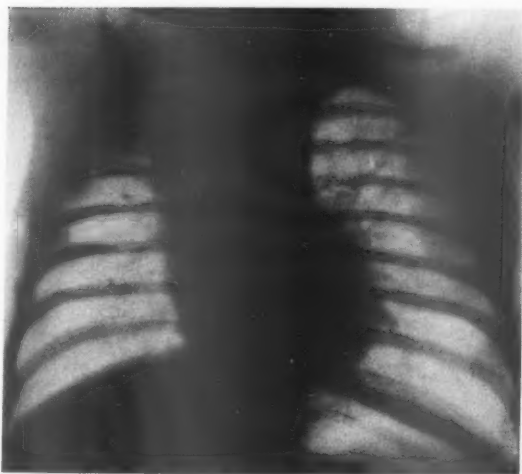
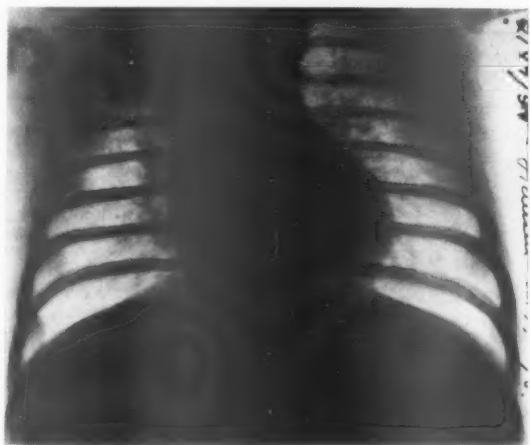
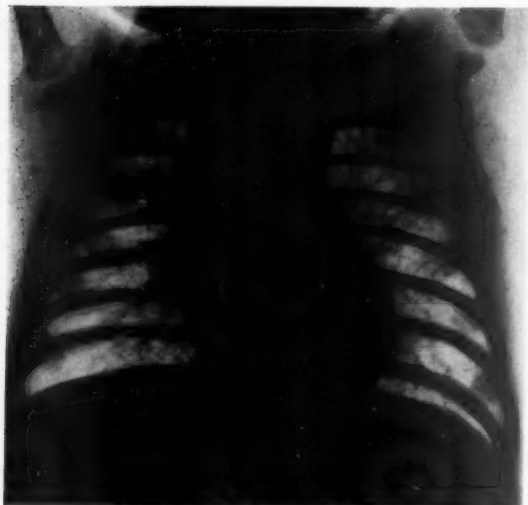


Fig. 2. Case 2. Girl, 2 months old.
a; Atelectasis of the right upper lobe (March 5).



b; 24 hours after bronchoscopy and aspiration (March 6).



c: 3 days later (after the 1st bronchoscopy with aspiration). Atelectasis all gone (March 8).



Fig. 3. Case 2. Secretion withdrawn at the 1st bronchoscopy.

12 hours later (March 6) the child appeared to be perfectly well, even though the nostrils were still distended a little. There was practically no respiratory retraction of the epigastrium and jugulum. On the following day (March 7) her condition was still satisfactory; respiration was free, without any retraction. *Auscultation of the lungs*: Distinct decrease in the dullness of the right side.

March 8: *Auscultation of the lungs*: No abnormality. *X-ray examination*: Atelectasis practically all gone (Fig. 2 c).

On discharge, after 11 days in hospital, the child was perfectly well.

The admission of these two patients within one month might be taken to indicate that *acute infectious atelectasis* is not altogether infrequent in infancy.

In order to look into the frequency of this lesion, therefore, we have gone through the autopsy records of the Pediatric Dept. of the Sundby Hospital and the Blegdam Hospital (Epidemic Diseases)¹ for the last 5 years of those children who died under the diagnoses of pneumonia, bronchitis or laryngo-tracheobronchitis fulminans.

The frequency of atelectasis is shown in Table 1.

Table 1.

Atelectasis demonstrated by autopsy in 178 children, who died under the diagnoses of pneumonia, bronchitis or laryngo-tracheobronchitis in 1945—49.

Age	Sundby Hospital				Blegdam Hospital			
	+ Atelectasis			No atel- ectasis	+ Atelectasis			No atel- ectasis
	focal	exten- sive	total		focal	exten- sive	total	
3 weeks—								
3 mths.	6	3	9	18	4	7	11	10
3-6 "	2	4	6	2	10	4	14	18
6-12 "	0	5	5	4	12	7	19	27
1-2 years	0	1	1	2	7	2	9	12
>2 "	0	0	0	2	1	1	2	7
Total	8	13	21 ² (43 %)	28 (57 %)	34	21	55 ³ (43 %)	74 (57 %)

¹ We are greatly obliged to Professor H. C. A. LASSEN, M. D., Chief of the Blegdam Hospital, for permission to make use of the case records.

² In 3 of these cases the clinical diagnosis was laryngo-tracheobronchitis.

³ In 2 of these cases the clinical diagnosis was laryngo-tracheobronchitis.



Fig. 4. Boy, 3 months old.

a: Atelectasis of right upper lobe (Sep. 26, 1948).

The figures given in Table 1 are the absolute minimal figures, as in a not inconsiderable number of these cases no histological examination was made, and atelectasis cannot always be distinguished from pneumonia by macroscopic examination alone.

In this material the diagnosis of atelectasis was made clinically only in *one* case—that of a girl, 3 months old, who was admitted to the Blegdam Hospital for whooping-cough. The diagnosis was made roentgenographically, and bronchoscopy was not performed. The child was treated with penicillin and alphasol but died 9 days after admission—complete atelectasis of the right lung developed gradually (Figs. 4 a and 4 b).

Among the 129 patients in the autopsy material from the Blegdam Hospital 1945–49 (cf. Table 1) X-ray examination was performed only on 2 other patients (2 boys, 5 and 8 months old). In each of these cases the X-ray diagnosis was pneumonia, but autopsy (carried out 1 and 2 days after the X-ray) revealed the



b: 8 days later. Total atelectasis of the right lung (verified on autopsy 24 hours later). Bronchoscopy not performed.

presence of atelectasis in both, and no pneumonia. At the X-ray examination no lateral picture was taken, and this may perhaps explain the erroneous X-ray diagnosis.

Etiology and Pathogenesis of Acute Infectious Atelectasis

The term "atelectasis" means areas in the lungs where the alveoli contain no air but have undergone pronounced retraction and shrinkage. The prerequisite of this condition is active contraction of muscle tissue in the lungs, which thus distinguishes atelectasis from simple collapse of the lung (XALABARDER, 1949).

Clear-cut atelectasis is merely a stage of brief duration that is followed by vasodilatation with production of a serous, sometimes hemorrhagic, intra-alveolar exudate that may become infected from the bronchi. Atelectasis is taken to be reversible at

any of these stages. If it becomes more protracted, however, fibrosis and bronchiectasis may develop in the affected area.

In many cases the atelectatic process is preceded by bronchial obstruction. But it is the general opinion that it may also develop without obstruction, presumably through reflex action combined with hypoventilation (XALABARDER, 1949). Atelectasis due to obstruction occurs most often in infants. For instance, ANSPACH (1939) states that 80 % of such cases of atelectasis are found in children under 2 years, but he does not offer any explanation of this. VAN ALLEN & Soo, on the other hand discuss this pointing out that "collateral respiration" may prevent the development of atelectasis, even though small branches of the bronchi be obstructed. In infants, however, the lungs contain relatively far more interstitial tissue than do the lungs of older children and adults, resulting in a lesser possibility of "collateral respiration", and this may perhaps explain the greater frequency of atelectasis in infants. Furthermore, the risk of bronchial obstruction is also greater in infants, because of the small dimensions of the bronchi and the inability of infants to cough and expectorate.

Symptomatology of Acute Infectious Atelectasis

Clinical

The predominant feature in these children is severe dyspnea with pronounced retractions of the epigastrium and jugulum, but no stridor. The chest is markedly distended, being almost fixed in the position of maximal inspiration, so that, in spite of the great efforts of the thoracic wall, the breathing becomes very shallow. On this account, as a rule, no râles are heard on auscultation. It is also a characteristic feature that the dyspnea does not satisfactorily improve with oxygen therapy—in contrast to pneumonia. The colour of the face is greyish, associated with a state of shock. Definite cyanosis therefore is not a dominant symptom, appearing only occasionally on marked physical exertion, *e.g.*, when the child is crying.

Cough may be entirely absent, but in typical cases a so-called

"frustrate cough" is present—*i.e.*, a dry, hacking, paroxysmal and ineffective cough.

The temperature is often normal or only slightly elevated—as seen in severely intoxicated children with pneumonia.

On *auscultation*—as in pneumonia—dullness, impaired respiration and râles may be demonstrated. But a sign of differential diagnostic significance is retraction of the affected side of the chest with displacement of the heart to the affected side, even though this as a rule may be ascertained only when the atelectasis involves the right lung, and with diminished excursions of the chest wall and, sometimes, the diaphragm kept at a high level.

Bronchoscopy shows a very abundant amount of mucopurulent secretion in the bronchi.

Roentgenological

The X-ray picture is characterized by a shadow produced by the retracted atelectatic area, with a sharp convex border. In addition, the trachea and the heart are displaced to the affected side. Further, the interlobar fissures are displaced, and the intercostal spaces diminished, sometimes with elevation of the diaphragm.

As these patients were markedly exhausted, the X-ray examination had to be performed in the ward. At first the roentgenograms were failures because the very rapid respiration (80—100 per min.) required a rather short time of exposure, and this was not practicable with the portable X-ray apparatus at our disposal. This difficulty was overcome, however, by means of a simple trick, *viz.*, by means of a pin-prick the child was made to cry, and after a few vigorous screams, the breathing stopped long enough for adequate roentgenography.

Discussion

The clinical picture just described as characteristic of acute infectious atelectasis differs from that of the typical acute fulminant laryngo-tracheobronchitis, above all, in the absence of any obstruction of the larynx, *i.e.*, dyspnea is the main symptom. On the other hand, it is well known that the occurrence of atelec-

tasis may also play an important role in laryngo-tracheobronchitis—first described by BRENNEMANN, CLIFTON, FRANK & HOLINGER (1938) in America, and later by BOYSEN & BOYSEN (1942) and ARNESEN, BJERKELUND & BØE (1947) in Norway, by SÖDERLING (1947) in Sweden, and by BRÆSTRUP (1948) in Denmark. All these authors also mention that in some cases of fulminant laryngo-tracheobronchitis the laryngeal obstruction may not be obvious or spontaneously subside completely, so that in these cases, too, a clinical picture develops in which "pulmonary dyspnea" results from obstruction of the deeper air passages and possibly the formation of this atelectasis is the dominating feature. However, this clinical picture is probably a rather uncommon variant of fulminant laryngo-tracheobronchitis. None of these authors differentiate acute infectious atelectasis without stridor as a nosographic entity *per se*, which the clinician has to keep in mind especially in the diagnosis and treatment of pneumonia.

DE BRUIN & GERLINGS (1937) have described the development of atelectasis after bronchitis and pneumonia in two older children. They were treated with bronchoscopy and aspiration, but only some weeks after the onset of the illness. These two cases therefore fall outside the clinical picture which we wish to point out as characteristic and distinct disease entity in infants.

It seems right to assume that the acute, *noninfectious*, atelectasis in the new-born ("amniotic fluid atelectasis") could also be treated in a similar way *i.e.*, by bronchoscopy.

Treatment

Aspiration of the secretion in the bronchi is the most important part of the treatment in that phase of acute infectious atelectasis where the dyspnea is most pronounced and the patient is threatened with suffocation. As described in our case histories, the *aspiration* should be performed in connection with peroral bronchoscopy. This causes minimum upset and is easy to perform within a few minutes with the child in bed. It is tolerated well even by moribund infants. The life-saving significance of this intervention was emphasized by its immediate effect on the condition of the

patients and by the aspiration of the surprisingly large amounts of secretion. It is to be emphasized that bronchoscopy with aspiration should be looked upon as indicated whenever the clinical picture is suggestive of infectious atelectasis, even though the presence of this condition has not been verified roentgenologically.

Tracheotomy, in our opinion, is contraindicated in children presenting this clinical picture, as there was no laryngeal obstruction, and because such an operation would mean an added strain upon the child that easily might prove fatal to these exhausted children.

In contrast, both *tracheotomy and aspiration* would be indicated in typical cases of fulminant laryngo-tracheobronchitis—as emphasized by JACKSON & JACKSON (1936), GITINS (1932), and others who later discussed this disease. From their works, it is evident that when tracheotomy is performed the aspiration is most often carried out in a “groping” fashion with a catheter inserted through the tracheal cannula. This technique must, no doubt, be looked upon as considerably less effective than aspiration through a bronchoscope. This latter method is also advocated by BRENNEMANN and collaborators whenever it is technically practicable, *i.e.*, when the instruments required and an experienced bronchoscopist are available.

In more serious cases of simple pseudo-croup tracheotomy will be sufficient in itself.

The treatment of severely ill children also requires, *besides bronchoscopy, intensive therapy against the infection, a sufficient supply of fluid, the re-establishment of the electrolyte balance*, possibly also blood transfusion in order to overcome the state of shock unquestionably present.

The combating of the infection ought to be started at once by treatment with antibiotics etc. in order to ensure the greatest possible effect, bearing in mind that the nature and resistance of the pathogenic bacteria in the given case are unknown. Naturally, the aspiration should be carried out under sterile conditions, so that the proper bacteriological examination of the secretion and

determination of the bacterial resistance may be carried out and further treatment based rationally on the results.

Our patients received both penicillin and streptomycin by injection and inhalation. The results of the cultures and the demonstration of the varying sensitiveness of the isolated bacteria to the antibiotics employed showed this combined therapy to be justified.

Conclusion

1. *Acute infectious atelectasis* is not a rare condition in infants in connection with bronchitis and pneumonia. Autopsy on 178 infants who died under the diagnoses of pneumonia, bronchitis or laryngo-tracheobronchitis revealed atelectasis in 43 % of the cases.

2. *The clinical picture of the lesion is so typical* that the diagnosis can be made with a fairly high degree of probability, even on ordinary physical examination, but its *verification requires X-ray examination* with a portable apparatus on account of the exhausted condition of these children.

3. *The most important therapeutic measure* is early bronchoscopy and the aspiration of the secretion in the bronchi, and immediate employment of antibiotics.

4. It seems rather likely that the relatively high death rate from pneumonia in infant in spite of treatment with penicillin and sulfa preparations is due to unrecognized—and therefore untreated—acute infectious atelectasis.

Summary

The development of acute infectious atelectasis is pointed out as a contributory cause of the strikingly high death rate from pneumonia in infancy. The records of two characteristic cases are reported. A brief review is given of the autopsy records for 178 children who died under the diagnoses of pneumonia, bronchitis or laryngo-tracheobronchitis, showing the presence of atelectasis in 43 %. The diagnosis and treatment are discussed. It is emphasized that administration of sulfa preparations and antibiotics is not sufficient, and that repeated *bronchoscopy with aspiration* is required in order to avoid suffocation in the most critical phase.

T. JERSILD et N. RISKÆR: *Atélectasie aiguë infectieuse.*

La survenue d'une atélectasie aiguë d'origine infectieuse est considérée comme une des étiologies expliquant l'importance frappante de la léthalité au cours de la pneumonie chez l'enfant.

L'évolution de deux cas caractéristiques est reportée.

Il est donné une courte revue de 178 comptes rendus d'autopsies d'enfants décédés avec le diagnostic de pneumonie, bronchite ou de laryngo-trachéo-bronchite, décelant la présence d'atélectasies dans 43 % des cas.

Le diagnostic et le traitement sont discutés. Il est souligné que l'administration de sulfamides et d'antibiotiques est insuffisante et qu'il est nécessaire de recourir à des *bronchoscopies répétées avec aspiration* afin d'éviter l'asphyxie au cours de la phase critique.

T. JERSILD und N. RISKÆR: *Akute infektiöse Atelektase.*

Die Entwicklung der akuten infektiösen Atelektase wird beschrieben als zusätzliche Ursache für die so grosse Letalität an Pneumonien im Säuglingsalter.

Die Krankengeschichten von 2 charakteristischen Fällen werden mitgeteilt.

Eine kurze Übersicht wird gegeben über die Autopsiebefunde von 178 Kindern, die starben mit der Diagnose Pneumonie, Bronchitis oder Laryngo-Tracheobronchitis. Bei 43 % wurde Atelektasen nachgewiesen.

Die Diagnose und Therapie werden erörtert. Es wird betont, dass die Medikation von Sulfapräparaten und von Antibiotica nicht genügt, und dass wiederholte *Bronchoskopie mit Aspiration* erforderlich ist, um Erstickung in der höchst kritischen Phase zu verhüten.

T. JERSILD y N. RISKÆR: *Atelectasis infecciosa aguda parecida a la bronconeumonía en niños.*

El desarrollo de la atelectasis infecciosa aguda se señala como una causa que contribuye a la mortalidad infantil, notablemente elevada en casos de neumonía.

Se describen dos casos característicos.

Se hace una breve exposición de la autopsia de 178 niños muertos bajo el diagnóstico de neumonía, bronquitis o laringo-traqueobronquitis, que muestra la presencia de atelectasis en el 43 % de los casos.

Se discute el diagnóstico y el tratamiento. Se subraya que la administración de preparaciones de sulfa y antibióticos no es suficiente y que se requiere la *broncoscopia con aspiración* repetida a fin de evitar la sofocación en la fase más crítica.

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The Morbid Anatomy of Erythroblastosis Fetalis and Its Relation to the Rh-Factor

by

S. RANSTRÖM

Interest in erythroblastosis foetalis has increased markedly since 1941 when LEVINE et al. discovered that Rh-isoimmunisation occurs in this disease. It is fairly generally accepted nowadays, that Rh-isoimmunisation between mother and foetus is the fundamental cause of erythroblastosis foetalis.

Since 1941 research on erythroblastosis has been almost exclusively along serological lines while the serologists and clinicians have taken comparatively little interest in the morbid anatomy of the disease. Some fairly extensive series of autopsy cases have been described during the last few years, namely those of GILMOUR, ZOLLINGER, MILLER, MACKLIN, JAVERT, and CLAIREAUX. The results of these authors contain some discrepancies which can hardly be interpreted otherwise than as being mainly due to different criteria for the selection of the cases, i.e., different criteria for the diagnosis of erythroblastosis foetalis.

If the selection is based solely on the clinical symptoms (hydrops, icterus and anaemia gravis) there must be many cases in which the differential diagnosis is difficult and there is a great risk that the material may include cases in which the symptoms were due to other causes, and also that some true cases of erythroblastosis foetalis may be excluded because death occurred before the symptoms had developed.

It is clearly not satisfactory to base the selection of cases solely on the presence of signs of Rh-isoimmunisation in the mother. Many of the children of immunised mothers show no

Extramedullary haematopoiesis was present to an abnormal degree in the present series, but it varied considerably in extent from case to case. It often led to enlargement of the liver and spleen (in case 12 and 13 there was rupture of the enlarged spleen).

Case No.	Sex	Preg-nancy No.	Siblings	Blood group			Rh-antibodies in the mother's blood	Diagnosis	Course
				M	Ch	F			
1 370/43	♀	4	1. and 3. dead perinatally	Rh—			blocking antibodies	Hypodrops	Dead sub partu
2 90/44	♂	1		Rh—	Rh+		blocking antibodies	Ict. grav.	Dead sub partu
3 54/46	♂	3		Rh—	Rh+		agglutinins	Ict. et an-aemia grav.	Dead 6th day
4 261/46	♂	6	5. stillborn (no diag.)	Rh—			blocking antibodies	Hypodrops	Dead 3rd day
5 339/46	♂	2		Rh—			agglutinins	Ict. et an-aemia grav.	Dead 3rd day
6 407/46	♀	6	2. dead (premature)	Rh—	Rh+		blocking antibodies	Ict. grav.	Dead 4th day
7 302/47	♀	1		Rh—	Rh+		agglutinins	Hypodrops	Dead 1 hour post partum
8 41/48	♂	3	2. = case No. 5	Rh—	Rh+		agglutinins	Hypodrops	Dead $\frac{1}{2}$ hour post partum
9 154/48	♀	3	2. dead 7th day (no diag.)	Rh—			agglutinins	Ict. grav.	Dead 2nd day
10 305/48	♀	4	3. ict. grav. (lives, healthy)	Rh—	Rh+		blocking antibodies	Hypodrops	Dead 2 hours post partum
11 77/49	♂	5	2. and 3. abortions	Rh—	Rh+		blocking antibodies	Hypodrops	Dead 2nd day
12 329/49	♀	2		Rh—			agglutinins	Ict. et an-aemia grav.	Dead 12 hours post partum
13	♂	1		Rh—			agglutinins	Hypodrops	Dead 2 hours post partum

M = mother. Ch = child. F = father.

The mean value for the weight of the liver in this series was 190 g and it represents 5.85 % of the body weight. POTTER & ADAIR give normal values of 150 g and 4.5 % for infants of comparable body weight. It would appear that hitherto the definition of erythroblastosis has been taken to include both extramedullary haematopoiesis and erythroblastaemia as essential features of the pathology. However GILMOUR, for example, has included in his series cases without extramedullary haematopoiesis. ZOLLINGER only included cases in which it was present, but his series included infants up to two months old. However, POTTER maintains that the extramedullary haematopoietic foci disappear soon after birth, having largely gone after the first few days of life.

The cellular composition of the haematopoietic tissue varies considerably from case to case. Sometimes the cells belong almost exclusively to the erythropoietic series, often there is a mixture of cells belonging to both the erythropoietic and leucopoietic series (erythroleucoblastosis) while, more rarely, the leucopoietic series may predominate (GILMOUR). GILMOUR considers that the haematopoiesis is of a type which occurs normally during the earlier part of foetal life. POTTER would appear to share this view with the reservation that she considers that the extramedullary haematopoiesis of erythroblastosis foetalis is more focal than the normal. This distinction, however, does not seem to the present author to be of general validity.

Most authors consider the extramedullary haematopoiesis to be a compensatory reaction to anaemia and increased destruction of blood. ZOLLINGER, on the other hand, thinks that it is a cellular reaction to the Rh-isoimmunisation, and thus comparable to the lymphocytic-plasma cellular reaction occurring in adults in the presence of antigen-antibody reactions. Both of these hypotheses about the mechanism by which the extramedullary haematopoiesis arises, are perfectly consistent with the theory that Rh-isoimmunisation is the fundamental cause of erythroblastosis foetalis. It should, however, be pointed out that extramedullary haematopoiesis may be found without any sign of anaemia. In such cases it may be assumed that the extramedullary haematopoiesis fully compensates for the blood destruction. It is, however, possible

that some other factor may be responsible for the occurrence of the extramedullary haematopoiesis.

The deposition of iron, particularly in the liver and spleen has been taken to be associated with the blood destruction caused by the Rh-antibodies. It is, however, sometimes found without any anaemia or other sign of haemolysis. ZOLLINGER found iron deposits in all of his cases while POTTER maintains that an absence of iron containing pigments does not by any means exclude the diagnosis of erythroblastosis foetalis. The present material accords best with POTTER's view as iron deposits were found in only 8 of the 13 cases.

Oedema is one of the main signs of hydrops foetalis. WIENER, among others, considers that it is due to increased capillary permeability caused by anoxaemia. ZOLLINGER attributes the capillary damage to the antigen-antibody reaction. KORDENAT and others think that the oedema is due to capillary damage caused by haemolysis. DAVIDSOHN attributes the oedema to both capillary damage and hypoproteinaemia, which factor is also cited by JACOBI et al. None of these interpretations are inconsistent with the theory that erythroblastosis foetalis is caused by Rh-isoimmunisation.

Liver damage in the form of necroses and fatty degeneration has been given the central position in the morbid anatomy of erythroblastosis foetalis by WIENER, DAVIDSOHN and others. It, rather than haemolysis, is considered to be the cause of the icterus (WIENER) and even of the hypoproteinaemia (JACOBI et al., LEONARD et al. and DAVIDSOHN). However, icterus may be found without obvious morphological signs of liver damage and vice versa. WIENER believes that the liver damage is caused by emboli of blood corpuscles agglutinated by the Rh-antibodies. ZOLLINGER attributes it to the antigen-antibody reaction, while POTTER considers it to be of minor importance. In the present series the damage to the liver cells did not appear, histologically, to be severe even in cases of icterus gravis.

Enlargement of the suprarenals has been described by several authors, e.g. LIEBEGOTT, BENEKE, SARASON, MACKLIN, MILLER, GILMOUR and JAVERT. SARASON and GILMOUR consider that the

characteristic change consists in an abundant deposition of lipoids in the boundary zone between the zona glomerulosa and the zona fasciculata. This type of lipoid deposition was found to a greater or lesser extent in all cases in the present material. POTTER and ZOLLINGER state that they were unable to demonstrate any characteristic changes in the suprarenals, but do not give any information as to the size of the suprarenals in their cases. In the present series the average weight of the suprarenals was 14.6 ± 2.7 g (4.41 ± 0.99 ‰ of the body weight). In a control series with comparable body weights collected in 1949 the figures were 8.0 ± 2.6 g (2.7 ± 0.59 ‰ of the body weight); these figures are in good agreement with those given as normal by POTTER & ADAIR. There is, therefore, ground for the belief that enlargement of the suprarenals, both absolute and relative to the body weight, is of very common occurrence in erythroblastosis foetalis.

Insular hyperplasia of the pancreas has been demonstrated by LIEBEGOTT, BENEKE, GILMOUR, MILLER, MACKLIN, and by POTTER "in a few instances." GILMOUR measured the diameter of the islets and found them to be enlarged in hydrops foetalis, while ZOLLINGER found no difference in insular diameter between cases of erythroblastosis foetalis and normal controls (the mean diameter was actually lower in the series with erythroblastosis than in the controls). ZOLLINGER did not estimate the number of islets in relation to the volume of the pancreas but states that he did not observe any notable increase in the number of islets. The rest of the authors mentioned did not count or measure the diameter of the islets but state that the hyperplasia was considerable. A similar considerable hyperplasia was found in 4 of the 13 cases in the present series. It took the form of crowding together of islets of various sizes and with nuclear polymorphism. It is very hard to arrive at a reliable estimate of the total amount of insular material. As has been pointed out, by FEYRTER among others, the islets are only part of the insular apparatus, insular tissue is to be found outside them as well. When the formation of such tissue is increased, numerous small islets are seen as well as an enlargement of the other islets. Measurements of the insular diameter in such cases are therefore likely to give a lower average value

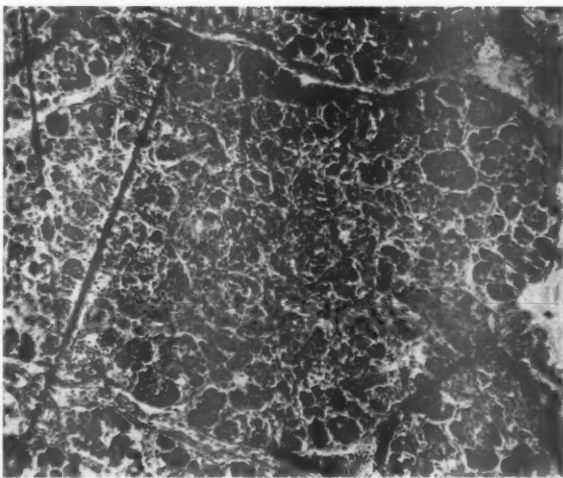
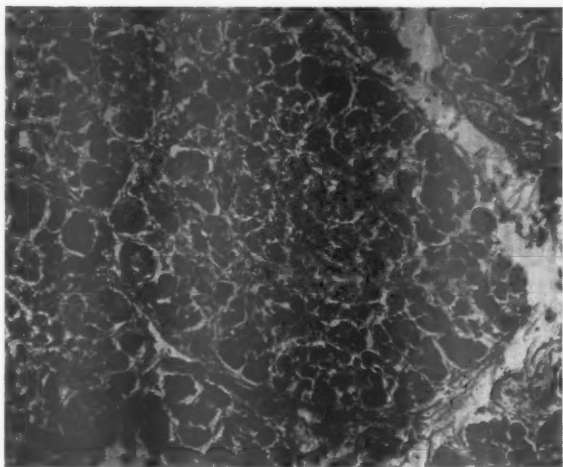


Fig. 1. Pancreas from cases 4 and 7 showing increase of interstitial cells especially in the centre of the lobulus (in case 7 with tendency to islets formation).

than the normal (cf. GÜTHERT, v. BAKAY). In 4 cases in the present series there was a striking increase in the interstitial cellular tissue between the tubules of the exocrine apparatus, with, here and there, a tendency to islet formation. These interstitial collections of cells are usually most frequent in the centres of the acini (Fig. 1). Their staining properties are similar to those of the insular tissue and argentophile α -granules are found in some of the cells. This increase in the number of interstitial insular cells was also more or less prominent in the 4 cases where there was insular hyperplasia. From the information available in the literature it is hard to judge how common insular hyperplasia of the pancreas is in cases of erythroblastosis foetalis. However, it can hardly be held to be rare.

As to the microscopical appearance of the *hypophysis*, it was stated in a previous communication (RANSTRÖM, 1945) that the only abnormality was an increase in the number of basophil cells which are normally only present in very small numbers, if at all,

Table 2.

Case No.	Body weight	Liver weight	Relation liver-body-weight (%)	Adrenals weight	Relation adrenals-body-weight (%)	Pancreas		Hypophysis	
						ins. hyp.	int. hyp.	eos. (norm. +)	baso. (norm. -)
1	3000	200	6.67	14.5	4.84	+	(+)	++	++
2	4170	160	3.84	12.1	2.90	—	+	+	+
3	3100	170	5.49	14.5	4.68	—	(+)	+	+++
4	4070	220	5.40	17.5	4.30	—	+	++	++
5	2680	120	4.48	10.0	3.73	—	—	+	+
6	3850	190	4.94	18.3	4.75	—	—	+	++
7	2840	210	7.40	13.6	4.79	—	+	++	++
8	3200	230	7.19	17.6	5.68	+	(+)	++	++
9	2770	185	6.69	16.7	6.03	—	—	++	++
10	3720	250	6.72	11.6	3.12	(+)	+	++	+
11	3950	260	6.58	14.4	3.65	—	—	++	++
12	3000	220	7.32	enlarged	—	+	(+)	++	+
13	3810	enlarged	—	enlarged	—	+	+		
Mean value....		192 ± 42	5.85 ± 1.18	14.6 ± 2.7	4.41 ± 0.99				
Control material				8.0 ± 2.6	2.74 ± 0.59				
POTTER & ADAIR		150	4.41	9.0	2.70				

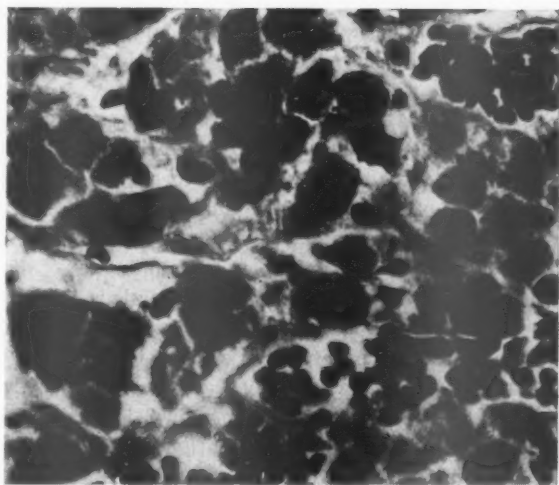
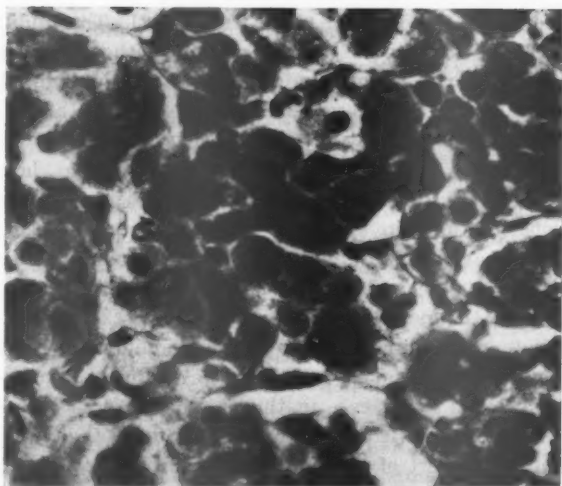


Fig. 2. Hypophysis from cases 2 and 7 showing premature differentiation with many eosinophil and basophil cells.

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in the new-born infant (cf. KRAUS, STÄMMLER). The findings in a control series collected by the present author support this view. However, as a rule, quite a number of eosinophil cells have already become differentiated by the time of birth. This means that an increase in the basophil cells is much more easily observed than an increase in the eosinophils. It seems, however, that, in some cases, there is a considerable increase in the eosinophils alongside the more strikingly apparent increase in the basophils. The changes in the hypophysis in erythroblastosis foetalis may therefore be generally described by saying that the chromophobe cells of the foetal hypophysis, with their scanty cytoplasm, differentiate prematurely to form the chromophil cells (Fig. 2). It was possible to demonstrate some degree of this premature differentiation in every case in the present material. The view thus seems to be justified that this abnormality of the hypophysis commonly form part of the morbid anatomy of erythroblastosis foetalis.

There is no account in the literature of any change in any of the other endocrine organs which can be definitely correlated with erythroblastosis foetalis, nor were such changes found in the present series. It is, however, generally stated that the thymus is often atrophic; this was evident in our cases.

It is quite clear that extramedullary haematopoieses, oedema, iron deposits and degeneration of the liver are not pathognomonic of erythroblastosis foetalis; these changes occur in many widely differing disorders of the newborn infant. Neither are the endocrine changes pathognomonic. Hyperplasia of the suprarenal cortex is seen in congenital syphilis and in the babies of diabetic mothers, in whom extramedullary haematopoiesis is also present. The insular hyperplasia both in the form of an increased number of islets and of increased proliferation of interstitial insular tissue is also known to occur in the babies of diabetic mothers (NEVINNY & SCHRETTTER) though not, so far as is known, in any other condition. Even the premature differentiation of the cells of the hypophysis has been described in these cases (NEVINNY & SCHRETTTER, OKKELS & BRANDSTRUP). It is worth mentioning in this connection that the similarity between congenital syphilis, the babies

of diabetic mothers and erythroblastosis foetalis extends to the appearance of the placenta (oedema, foci of blood formation, persistence of the cellular layer of Langerhans, degeneration of the syncytial layer and fibrosis, cf. HELLMAN & HERTIG). It is therefore clear that the conditions from which erythroblastosis foetalis must be differentiated are primarily congenital syphilis (cf. POTTER's extensive discussion) and diabetes of the mother. In congenital syphilis there are, of course, usually other stigmata which clinch the diagnosis, as well as serological information about the mother. The differential diagnosis from maternal diabetes is more difficult. As MILLER et al. and JAVERT et al. have pointed out, it is often impossible to distinguish between cases of erythroblastosis foetalis and children of diabetic mothers on morbid anatomical grounds. The difficulties of differential diagnosis are not removed by finding out whether the mother is diabetic or not. MILLER has reported apparently healthy women who gave birth to erythroblastotic infants and later developed diabetes. In these cases it may be said that the erythroblastosis of the babies was an early symptom of the mother's diabetes.

As was pointed out earlier, the current interpretations of the first group of morbid anatomical features of erythroblastosis foetalis (i.e., extramedullary haematopoiesis, oedema, liver damage, and iron deposits) are consistent with the theory that Rh-isoimmunisation is the fundamental cause of the condition. The position is, however, rather different as concerns the endocrine changes. The view was expressed in the previous communication (RANSTRÖM 1945) that these could not reasonably be considered to be caused by the Rh-isoimmunisation. This view, however, must now be modified. SELYE (1946) has observed changes in the endocrine organs in what he calls the "general adaptation syndrome", i.e., the reaction of the organism to all kinds of toxic or stress factors. The pathological syndrome thus produced includes hyperplasia of the suprarenal cortex, increase in the basophil cells of the hypophysis, atrophy of the thymus, and degeneration of the liver, all of which also form part of the pathology of erythroblastosis foetalis. It is possible that a continuous antigen-antibody reaction occurring as a result of Rh-antibodies constantly

reaching the foetus from the mother may be comparable with the conditions obtaining in SELYE's experiments. Erythroblastosis foetalis may therefore be a manifestation of the adaptation syndrome in association with haemolysis caused by the Rh-antibodies. On the basis of such a hypothesis the whole morbid anatomy of erythroblastosis foetalis could be explained theoretically as having been caused by Rh-isoimmunisation. This would fulfil the first condition for acceptance of the theory that Rh-isoimmunisation is the fundamental cause of erythroblastosis foetalis.

The second condition for acceptance of the Rh-theory is that it should be possible to explain the clinical course of the condition in terms of Rh-isoimmunisation. This aspect of the matter has, up till now, presented great difficulties. LEVINE, the originator of the theory, does not seem to have made any attempt to explain why "*in the vast majority of the cases the course of the pregnancy and delivery is entirely normal.*" The dangerous symptoms do not arise until during or after birth, i.e., not until the foetus is separated from the mother who is the source of the harmful substances—a time when one might have expected improvement to occur. LEVINE has even admitted that "*the method employed to supply the evidence for the pathogenesis of erythroblastosis foetalis is mainly statistical.*" DIAMOND has stated that he can give no explanation as to why the symptoms set in so late. To judge from the available literature, WIENER is the only person who has tried to give a theoretical explanation of the clinical course of the disease on the basis of the Rh-theory. In some of his later communications, however, WIENER seems to have departed from his theory to some extent, and it would appear that he now considers that the blocking antibodies are the cause of erythroblastosis foetalis while the agglutinins are of lesser significance.

It appears clear that it is not possible to arrive at a satisfactory explanation of the clinical course of erythroblastosis foetalis solely on the basis of Rh-immunisation. However, if the morbid anatomy is also taken into consideration, it would appear possible to arrive at last at a *hypothetical* explanation as to why the dangerous symptoms do not appear till birth or shortly afterwards. The morbid anatomical changes clearly develop before

birth. It would seem probable that these changes in the foetal endocrine organs are accompanied by corresponding functional disturbances. It may be supposed that both hypo- and hyperfunction of the foetal endocrine organs can be compensated for by inflow and outflow of hormones through the placenta, as happens, for example, in pregnancy in diabetic women. At birth, when the safety valve formed by the placenta is suddenly closed, the clinical symptoms of the disordered function of the endocrine organs become manifest. The symptoms and risks vary according to the organ affected and the degree of disturbance.

In the above discussion an attempt has been made to interpret the morbid anatomy and clinical course of erythroblastosis foetalis on the basis of the theory that Rh-immunisation is the fundamental cause of the disease. The two assumptions made above, that the endocrine disorders are a manifestation of the adaption syndrome and that they are the reason why the symptoms do not begin till birth or afterwards, would reconcile the Rh-theory with the morphological changes and clinical course of erythroblastosis foetalis. It must, however, be mentioned that some observations have been made which do not fit in with the Rh-theory.

There is, undoubtedly, a group of cases of erythroblastosis foetalis in which there is no basis for Rh-isoimmunisation, and where syphilis and manifest diabetes of the mother can be excluded. The present author has seen four such cases where the clinical and morbid anatomical pictures were typical of erythroblastosis foetalis. In two of these cases the patients were siblings, and in a third, two previous siblings had suffered from icterus gravis during the neonatal period. Judging from the literature this group would appear to comprise about 10 % of all cases of erythroblastosis foetalis and is therefore not an insignificant group. It is true that the literature contains references to cases in which erythroblastosis foetalis was considered to be due to the A or B blood group factors. These cases, however, seem to be very rare although the conditions for blood group isoimmunisation within the ABO system must occur far more often than those for Rh-isoimmunisation, and in spite of the fact that the preformed anti-

A and anti-B agglutinins are considerably more active than the Rh-antibodies.¹

MAYES has collected a series of 572 deliveries in which the mother was Rh(-). In about half of the cases the baby received a blood transfusion from the mother by the cord. In the other half blood from an Rh(-) donor or from the father was given by the same route. No deaths occurred in the first group while 5 occurred in the second, 4 after the administration of Rh(-) donor's blood. This result is clearly diametrically opposed to what would have been expected. According to the Rh-theory transfusion of maternal blood should be the worst possible treatment. MAYES draws the following conclusion:—*'We have been led to believe that the Rh-factor, although important, in erythroblastosis foetalis, is not the exciting factor.'*

In this connection CHOWN's observations are of interest, viz., cases in which immunised Rh(-) women, who had previously given birth to erythroblastotic babies, later had healthy Rh(+) babies in spite of the presence of Rh-antibodies in the maternal blood. Identical observations were made by DONOHUE & FREMES. CHOWN concludes that *'other factors than blood group incompatibility play an important, at times a deciding, role in the development or non-development of erythroblastosis'*. It may also be mentioned here that PICKELS has found Rh-antibodies in the blood of a healthy, new-born Rh(+) child of an immunised Rh(-) mother.

Of great interest in this connection are DIAMOND's recently published observations. In a series of about 200 cases of erythroblastosis foetalis some three-quarters were transfused with blood from male donors, the rest were transfused with female blood. In the first group the mortality was 19.7 %, in the last one there was no fatal case. DIAMOND believed that there is some substance

¹ It may be pointed out in this connection that clinical experience suggests that the administration of anti-A and anti-B agglutinins does not produce serious effects, members of group O being used as universal donors; it is the transfusion of incompatible A or B corpuscles which is the major cause of complications after transfusion. If this is applied to the Rh-factor it would be expected that an Rh(+) foetus would not be seriously harmed by the Rh-antibodies reaching it. Perhaps, though, it is not legitimate to compare single large transfusions with the continuous inflow of comparatively small amounts of agglutinins.

in the female blood responsible for the therapeutic effect. DIAMOND's and MAYES' results are clearly in good agreement with each other. Perhaps this by DIAMOND suggested substance is the factor searched for by MAYES and CHOWN, and perhaps it is of endocrine nature, a possibility which is intimated in DIAMOND'S description. As a matter of fact there are in the literature suggestions that endocrine substances may be of importance in the development or non-development of erythroblastosis fetalis (e.g., BOEHNCKE, DE SNOO, BROMAN).

It has been established that the amount of Rh-antibodies in the maternal blood bears no relationship to the severity of the disease in the foetus or child, and, furthermore, that the average antibody content of the maternal blood is not greater in later than in earlier pregnancies (BOORMAN et al., GAMMELGAARD). There is, nevertheless, an unmistakable tendency for the symptoms to be more severe and the mortality greater in later than in earlier pregnancies. This fact also supports the view that factors other than Rh-immunisation also play a part in the origin of erythroblastosis foetalis. (Assuming an endocrine factor in the causation of erythroblastosis foetalis it might be supposed that the extra strain placed on the endocrine system by each succeeding pregnancy would lead to an increase in the risk to the foetus, as has been previously suggested by HERLITZ.)

All of these observations which do not fit in with the Rh-theory might lead to the supposition that Rh-immunisation is merely a sign of placental damage, which allows of the passage of red blood cells and thus makes Rh-immunisation possible [cf. MILLER's statement that Rh-isoimmunisation seems to occur in all cases of pregnancy in Rh(-) diabetic women where the foetus is Rh(+)], and that the immunisation in itself has no harmful effect on the foetus. However, the incidence of Rh-immunisation is so high in erythroblastosis foetalis that it is only reasonable to conclude that Rh-immunisation itself has some clinical and pathological significance, whether it is, in fact the fundamental cause of the disease or only becomes possible as the result of some other disturbance causing damage to the placenta.

It is to be hoped that future research into erythroblastosis

foetalis will not be confined to the serology, but that interest will also be taken in the other problems such as the endocrine disturbances. The elucidation of these might form the basis for new, and possibly more effective and perhaps also prophylactic treatment. For, *in spite of the discovery of Rh-immunisation, erythroblastosis foetalis remains a problem.*

Summary

An autopsy series of 13 cases of erythroblastosis fetalis is reported. In this series there was increase of the adrenal weight, premature differentiation of eosinophil and basophil cells of the hypophysis, insular hyperplasia (4 cases) and increase of interstitial insular cells without islets formation (4 cases) in the pancreas. The morphological changes are discussed. The two assumptions that the endocrine disorders are a manifestation of the adaptation syndrome and that they are the reason why the clinical symptoms do not begin till birth or afterwards would reconcile the Rh-theory of the etiology of erythroblastosis fetalis with the pathological anatomy and the clinical course of the disease.

S. RANSTRÖM: *L'anatomie pathologique de l'érythroblastose foetale et sa relation avec le facteur Rh.*

On rapport une série d'autopsie de 13 cas d'érythroblastose foetale. Dans cette série, il y avait une augmentation du poids des surrénales, une différenciation précoce des cellules éosinophiles et basophiles de l'hypophyse, une hyperplasie des ilots de Langerhans (4 cas) et une augmentation des cellules interstitielles insulaires sans formation d'ilots (4 cas) dans le pancréas. Les changements morphologiques sont discutés. Les 2 suppositions que les désordres endocriniens sont une manifestation d'un syndrome d'adaptation et qu'ils sont la raison pour laquelle les symptômes cliniques commencent à la naissance ou après doivent réconcilier la théorie du facteur Rh comme étiologie d'érythroblastose foetale avec l'anatomie pathologique et la description clinique de la maladie.

S. RANSTRÖM: *Die pathologische Anatomie von Erythroblastosis foetalis und ihr Verhältnis zum Rh-Faktor.*

Es wird berichtet über eine Serie von 13 Fällen mit Erythroblastosis foetalis, die zur Obduktion kamen. Es fanden sich Vermehrung des Nebennierengewichts, premature Differenzierung der eosinophilen und

basophilen Hypophysenzellen, Inselhyperplasie (4 Fälle) und Vermehrung der interstitiellen Inselzellen ohne Inselbildung (4 Fälle) im Pankreas. Die morphologischen Veränderungen werden besprochen. Die beiden Annahmen, dass die endokrinen Störungen eine Manifestation des Adaptationssyndroms, und dass sie die Ursache dafür sind, dass die klinischen Symptome erst bei der Geburt oder danach beginnen, würde die Rh-Theorie von der Ätiologie der Erythroblastosis foetalis in Übereinstimmung bringen mit der pathologischen Anatomie und dem klinischen Verlauf der Erkrankung.

S. RANSTRÖM: *La anatomia patologica de eritroblastosis fetalis y su relación al factor Rh.*

Se informa sobre una serie de autopsias en 13 casos de eritroblastosis en el recién nacido. Se ha notado un aumento de peso en las glandulas adrenales, distinción prematura de eosinófilos y basófilos en la hipófisis, hiperplasia insular (4 casos) y aumento de células insulares en el intersticio del pancreas sin formación de islas (4 casos). Se discuten los cambios morfológicos. Se piensa que los dos conceptos señalando los desordenes endocrinales como manifestación del síndrome de adaptación y como causa de los síntomas clínicos que no aparecen hasta el nacimiento ó posteriormente, ponen de acuerdo el factor Rh en la génesis de eritroblastosis neonatorum con la anatomopatología y curso clínico de la enfermedad.

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Hypertrichosis in Childhood

A Clinical Study

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Hypertrichosis in adults has formed the object of numerous studies, but its appearance in childhood has attracted little attention and references to it in paediatric literature are scanty. Hypertrichosis in this age group has mostly been described as a sign in cases of gross endocrine disturbance, such as that associated with neoplasms of the adrenal cortex or of the hypothalamus. Its appearance in these patients has generally been attributed to an overproduction of androgenes in the adrenal cortex. Commonly the excessive growth of hair is but one of many characteristic manifestations of adrenal involvement, though on rare occasions it may achieve such prominence that it presents an unusual differential diagnostic problem. It therefore seemed desirable to study the normal hair distribution in healthy infants and children as well as pathological hairiness not obviously connected with endocrine dysfunction. Observations were carried out on several hundreds of healthy infants and children up to the age of fourteen years.

Physiologically lanugo covers the body of the premature or immature infant to a large extent, but occasionally it is found on the limbs and shoulders of the full term, normally developed and healthy newborn. The lanugo covering persists for several weeks and is then gradually lost.

Between three and six years of age a large number of children, irrespective of their hair colour and sex, show transitional hair growth of a fairly constant distribution similar to that of the adult.



Fig. 1. M. S. 3 years.
Familial hypertrichosis.



Fig. 2. B. S. 7 years.
Familial hypertrichosis.

On the upper limbs it covers the outer aspect of the forearm and lower third of the upper arm and on the lower extremity it appears on the anterior aspect of the lower legs extending up to approximately the middle of the thigh. At school age, however, this hair distribution is less frequently seen and hair growth is found on the body mainly localised in the interscapular area spreading occasionally to the skin over the scapulae. Sometimes interscapular and limb hair growth occur together. Transitional hair is replaced after puberty by the final hair of the adult.

Primary Hypertrichosis

Abnormal hairiness may be present at birth or develop soon after and then persist for life, as in the so called "dog-faced" or "Russian man." Such a case of the *congenital type* of generalised hirsuties in infancy with a peculiar arrangement of the hair was recently described by BROSTER (1950). It affected only the youngest of five brothers.

Occasionally the condition occurs in several members of a family (*Familial Hypertrichosis*). Recently one such family was seen in which the father and two sons were affected. The distribution of the hair was practically identical in all three cases. One of the sons, aged three and a half years, was admitted to Hospital on 27.1.50 with an acute glomerulo-nephritis. In the course of the examination hirsuties affecting the back and the extensor and lateral aspects of the limbs was noticed. The hair covering the arms was thicker than that on the legs. On the back the greatest hair density was localised at the height of the upper angle of the scapulae and in the lower lumbar region above the buttocks. The hair was directed downwards and medially, as if to converge at the mid-line; over the spine, shoulders and limbs no characteristic arrangement was noticeable (Fig. 1).

After recovery he was discharged home 23.3.50. The two other members of the family then presented themselves for examination. One aged seven years, a healthy boy, showed the hypertrichosis more marked than his younger brother, particularly over the limbs (Fig. 2). According to the parents' statement the younger child did not develop his hypertrichosis until two years of age, whilst the older was hairy from birth. The father of the two boys had a much heavier growth of hair than his sons.

Secondary Hypertrichosis

Transient hypertrichosis of various degrees appears to be more common in infancy and childhood than is generally realised. FEER (1947) mentions its occurrence in tuberculosis and in cachectic states in older children. The condition has recently been encountered in cases of pink disease, haematogenous forms of tuberculosis, coeliac disease and in one case of marasmus.

Pink Disease

A femal infant born on 13.7.48 of healthy parents was brought to the Out-patients' Department on 7.4.49 with the history that for the past two months she had not been well. On examination she presented the typical signs of acro-dynia.

On the 21.4.49 the infant developed chicken pox. After the eruption the sweating and the sweat rash subsided completely. A fortnight later the baby was seen again, perspiration was as bad as before the chicken pox infection, and noticeable hypertrichosis had developed involving the face, including chin, back, lateral aspects of the thorax, upper arms and thighs (Fig. 3). Lower arms and legs were free from excess of hair. After



Fig. 3. Hypertrichosis and Pink Disease.

a further fortnight the hirsuties had extended to the distal parts of the limbs. Only the abdominal wall, front of the chest, hands and feet remained free from the abnormal hair covering. In the course of the following month the hypertrichosis increased in density and the long downy hair formed a little goat-beard in the submental region. The appearance of the infant was strangely suggestive of a little monkey, particularly as the thick downy growth covered forehead, cheeks and chin completely. The baby was seen at regular intervals and during the following three months the hypertrichosis receded gradually, freeing at first the forehead and distal parts of the extremities, then the face and upper limbs; persisting longest on the interscapular area, over the shoulders and the face in the preauricular region. Six months after the onset of the hypertrichosis it had completely cleared, as had also the signs of acrodynia.

Another infant aged two years, had been suffering from pink disease for four months; hypertrichosis of the limbs and lumbar region developed during the last month. It subsided after a further three months.

Tuberculosis

Six cases showing hirsuties were observed, two with miliary tuberculosis, four with tuberculous meningitis. The most characteristic is described in detail.



Fig. 4. Hypertrichosis in tuberculosis showing the dense growth on the lower limbs.



Fig. 5. Hirsuties of face in tuberculosis.

A boy aged four years was admitted on 13.1.50. The clinical diagnosis of tuberculous meningitis was confirmed by the characteristic C.S.F. findings, positive culture for tubercle bacilli and the presence of chorioidal tubercles.

The child had been ill for two months before admission with loss of appetite, listlessness and feverishness.

In April 1950 (six months after the onset of the disease) hypertrichosis was first noticed. Distribution of the chestnut brown hair was as follows: there was fine lanugo-like hair on the face, more marked in the preauricular area, but covering most of the cheeks, extending to the submental region and lateral aspects of the neck. Only slight excess of hair growth was noticeable in the interscapular and dorso-lumbar regions, leaving most of the frame anteriorly as well as posteriorly free, though the lateral aspects showed scanty hair covering. The limbs were densely covered with transitional hair, particularly the outer aspects of the arms in their entire length but increasing in thickness distally. The legs showed most of the hair on the lateral and posterior aspects of the calves and the distal two thirds of the thigh, with the exception of the medial aspects (Fig. 4 and 5). The hair on the flexor surface of the thigh was pointing downwards; on the extensor surface it was directed upwards. This patient died on 5.7.50.



Fig. 6. Hypertrichosis on the lower limbs in coeliac disease.



Fig. 7. Hypertrichosis on back in a case of marasmus. Still visible during the stage of recovery.

Coeliac Disease

Three cases of coeliac disease showing hypertrichosis came under observation; the description of the most marked one is given in detail.

A male infant born on 9.9.45 of healthy normal parents was admitted for the first time to Hospital on 22.1.47 at the age of sixteen months. The history was characteristic and the clinical findings typical.

The course of the disease was stormy; phases of improvement were often followed by severe relapses; various deficiency states developed in the course of his illness. In the past five months improvement was maintained. Marked hypertrichosis was first noticed ten months ago after two and a half years of illhealth, at which time he presented the picture of a severe form of gastrointestinal infantilism. The hypertrichosis involved the forehead, preauricular region, the dorsum and, most strikingly, the upper and lower limbs, the density of the hair growth on the extremities increasing distalwards (Fig. 6). During the past three months of observation, the hirsuties has been rapidly clearing.

Two others, a fifteen months old female infant and an eighteen

months old male, suffering from a severe degree of infantile steatorrhoea, presented a form of hypertrichosis similar to the above, the hirsuties affecting particularly the face and forehead.

Marasmus

A female infant aged eighteen months was one of four siblings, the three others being perfectly healthy and not revealing any excess of hair growth. She was breastfed and developed normally till seven months of age. Because of weaning difficulties (she refused solids and reacted to compulsion with vomiting), breastfeeding was continued until her admission to hospital at the age of thirteen months. Her weight was then seventeen pounds, not much more than it had been at six months of age. She improved a little but contracted whooping cough and the vomiting was then so pronounced that she became grossly undernourished and her weight fell to about fourteen pounds. It took over two months to re-establish normal feeding habits after the whooping cough had ceased. It was then noticed that she showed a definite increase in body hair, which was of a fine lanugo-like structure covering the whole of the body but showing definite aggregation on the lower limbs (Fig. 7). This is the second case in this series to show hair covering of the anterior chest wall.

This infant is now getting over her feeding problems and gaining weight—the hypertrichosis is also diminishing.

Comment

Hypertrichosis in infancy and childhood seems to fall into two main groups for which the following classification is suggested.

- I *Primary* a) congenital
b) familial.
- II *Secondary* (or transient) associated with
 - a) endocrine disorders
 - b) acrodynia
 - c) coeliac disease
 - d) haematogenous forms of tuberculosis
 - e) marasmus
 - f) ? other conditions.

The congenital type has been regarded by some authors (DANFORTH 1925 and BROSTER 1950) as an instance of atavism. WOOD-

JONES pointed the interesting fact out that in man the free tips of the hair on the back converge towards the spine whilst in all other mammals the spine forms a watershed from which the hair diverges towards the flanks. Heredity is certainly an important factor in the development of the familial form.

Analysing the common factors in the cases of transient hypertrichosis described here, the outstanding feature is its development in diseases of relative chronicity, pink disease, coeliac disease and athrepsia. Tuberculous meningitis as well as miliary tuberculosis has, since the introduction of streptomycin therapy, changed from an acute disease into a chronic one. Malnutrition, though certainly present in the coeliac cases and the marasmic infant, was in no way prominent in the tuberculous or acrodynic cases. On the contrary the patients in the last two groups were reasonably well fed, with a fairly normal panniculus adiposus.

There is, however, no doubt that the hypertrichosis manifested a definite relationship to the progress of the primary disease. It developed in all cases only after the underlying disease process had been active for several months, rapidly reached its maximum and showed regression with improvement in the basic condition.

FONO (1949) suggested streptomycin as a possible aetiological agent, after observing hirsuties in twenty-seven children (fifteen boys and twelve girls) with miliary tuberculosis and tuberculous meningitis. He noticed its appearance after six to eight weeks treatment. This hypothesis is most improbable since hirsuties in tuberculosis had been noticed before the advent of streptomycin, and also since a number of our cases displaying excessive hair growth had never received any antibiotic or, indeed, any chemotherapy at all.

It seems of interest that the most marked hypertrichosis developed in a child with severe manifestations of acrodynia, where perspiration and acrocyanosis, as well as hypotonia, were the most troublesome features. As these indicate an involvement of the vegetative nervous system it appears feasible also to credit the involuntary nervous system with some role in the production of

this sign. Though the vegetative nervous system is implicated to some degree in every case of pink disease hirsuties seems rare.

Disturbance of the vegetative nervous control plays certainly some part in the clinical picture of coeliac disease; the frequent presence of vasomotor lability and excessive sweating has been attributed to vegetative dysfunction.

ZELLWEGER and LAUCHLI (1950) in a follow up study of coeliac patients treated at the Children's Hospital in Zurich between the years of 1918 and 1932 examined 22 of them, aged seventeen to thirty years. A number of these showed increased neuro-vegetative lability such as orthostatic hypotension, dermatographism, increased perspiration, mechanical hyperexcitability of peripheral nerves etc. One could therefore postulate the hypertrichosis as another derangement of the central or peripheral autonomic nervous system. The presence of *tache cérébrale* in tuberculous meningitis also points to some alteration of the vegetative control.

HOFF (1950) collected evidence demonstrating dependence of hair growth upon the nervous system and vegetative centres in the hypothalamus, though not underestimating the hormonal mechanism regulating it. HOFF and RIEHL (1937) found total alopecia in a case with a destructive process in the hypothalamus.

SCHALENBRAND (1949) observed marked difference of the hair distribution in cases of syringomyelia, sharply limited to one half of the body with absence of sweat secretion on the less hairy side.

The sexes seemed almost equally represented in this series, and there was no prominence of a definite hair colour, though the hypertrichosis in dark-haired children was more readily noticeable. The ages of these patients ranged from twelve months to ten years and no cases have yet been seen under twelve months of age though FEER refers to its occurrence in infants with pyloric stenosis.

Excessive hair growth in the children described in this paper was not limited to the normally hairy parts of the body but involved areas of skin which are physiologically free from it, such as forehead, cheeks, submental region and anterior chest wall.

Recession of the hypertrichosis seemed to take place in the inverse order of its appearance, so that regions of the body surface involved last were also first to lose their hair coat.

There was no form of hirsuties characteristic for any of the disorders implicated.

My thanks are due to Professor Wilfrid Gaisford for his helpful criticism.

Summary

1. Physiological hair distribution in infancy and childhood is discussed.
2. A familial form of hirsuties is described.
3. Transient hypertrichosis in cases of tuberculosis, coeliac disease, marasmus and acrodynia has been noted. Excessive hair growth in pink disease and coeliac disease has not previously been reported.
4. A clinical classification of hypertrichosis in childhood has been proposed.

A. HOLZEL: *Hypertrichoses de l'Enfance. Étude clinique.*

1. On y discute la distribution pileuse physiologique de l'enfance et de la jeunesse.
2. On y décrit une forme familiale d'hirsutisme.
3. On y note une forme d'hypertrichose transitoire dans des cas de tuberculose, maladie coeliaque, marasme et acrodynie. Cas de maladie coeliaque et d'acrodynie avec une poussée pileuse excessive n'ont pas été rapportés antérieurement.
4. On propose une classification clinique des hypertrichoses de l'enfance.

A. HOLZEL: *Die Hypertrichosis im Kindesalter. Eine klinische Studie.*

1. Erörterung der physiologischen Behaarung im Kindesalter.
2. Beschreibung einer sippengebundenen Art von Hirsutismus.
3. Bisher beobachtete man vorübergehende Hypertrichosen bei Fällen von Tuberkulose, Cöliakie, Marasmus und Akrodynie. Übermäßiger Haarwuchs bei Feer'scher Krankheit und Cöliakie wurde bisher noch nicht beschrieben.
4. Vorschlag einer klinischen Klassifizierung der Hypertrichosis im Kindesalter.

A. HOLZEL: *Hipertrichosis en la infancia*. Estudio clínico.

1. Se discute la distribución fisiológica de los pelos en la primera infancia y en la infancia.

2. Se describe una forma familiar de hirsutismo.

3. Se observa una hipertrichosis pasajera en casos de tuberculosis, de enfermedad celiaca, de marasmo y de acrodinia. No se ha podido reportar anteriormente crecimiento excesivo de pelo en la acrodinia ni la enfermedad celiaca.

4. Se ha propuesto una clasificación clínica de la hipertrichosis en los niños.

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La réaction diagnostique de BCG (Ustvedt)

par

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Lorsque, au commencement du 19^{ème} siècle, EDWARD JENNER s'occupait de la vaccination contre la variole il trouva que des individus qui avaient antérieurement été atteints de la maladie, réagissaient localement lors d'une nouvelle infection beaucoup plus rapidement que si l'infection avait lieu pour la première fois. Cette différence de réaction après une première infection fut oubliée. En 1891 elle fut de nouveau découverte dans la tuberculose par KOCH, et reçu à cause de lui, le nom de phénomène de Koch.

KOCH (1) donne de façon concise la description suivante: si l'on inocule à un cobaye sain une culture pure de bacilles tuberculeux la plaie guérit généralement dans les premiers jours, mais après 10—14 jours il se forme une grosseur sous-cutanée qui se nécrose en plaie ouverte qui subsiste jusqu'à ce que l'animal meurt de l'infection tuberculeuse. Les choses se passent de tout autre manière si l'on fait une nouvelle inoculation à un cobaye déjà tuberculeux. Dès le premier ou le deuxième jour il se forme une induration à l'endroit de l'inoculation, et celle-ci croît les jours suivants jusqu'à une grosseur de 0,5 à 1,0 cm, et se nécrose, produisant une plaie bien limitée. Cette plaie se guérit relativement vite. Les bacilles tuberculeux produisent donc des réactions différentes chez les cobayes sains ou tuberculeux. Cet effet n'est pas seulement atteint avec des bacilles vivants mais aussi avec des bacilles morts.

Le phénomène de Koch a dans la suite été l'objet d'études approfondies. Les doses de bacilles vivants utilisées par KOCH à la réinfection étaient d'un ordre de grandeur tel qu'elles produ-

isiaient des nécroses et des plaies suppurantes. Cependant plus tard on a trouvé (2) que le degré de la réaction dépend du nombre de bactéries inoculées: plus grand est celui-ci, plus grandes sont les réactions locales. Si la dose est petite il se produit seulement une induration et une rougeur à l'endroit de l'inoculation, c'est-à-dire la même réaction mais d'un ordre de grandeur moindre. USTVEDT (3), qui a spécialement étudié cette question, préfère n'employer l'expression «phénomène de Koch» que pour la réaction classique de violence plus grande, avec ulcération et suppuration. Pour les réactions locales plus faibles il emploie les termes «réaction locale accélérée».

Les circonstances sont les mêmes avec les bactéries BCG qu'avec les bactéries tuberculeuses virulentes dans les examens de KOCH. Lorsqu'un individu ne réagissant pas à la tuberculine est vacciné avec des bactéries BCG on observe, seulement deux à trois semaines après, une réaction locale à l'endroit de l'inoculation, que celle-ci ait été faite par injection scarifiée, multi-punctuaire ou intradermique. Mais si l'individu a été antérieurement traité par le vaccin BCG ou est devenu positif par infection, il survient lors d'une nouvelle inoculation de bactéries BCG une réaction locale dès le cours de la première semaine. Peut-être est-il intéressant de collationner le phénomène de Koch et la réaction locale accélérée avec les observations de STRÖM dans ses essais avec des BCG «marqués» radioactivement (9). Par injection sous-cutanée de ceux-ci à une personne négative à la tuberculine les bactéries se répandirent rapidement dans les ganglions lymphatiques régionaux tandis que chez des personnes sensibles à la tuberculine ils restèrent plus longtemps à l'endroit de l'inoculation.

USTVEDT, ANDENES et d'autres se sont au cours des dernières années intéressés au phénomène de Koch et à la réaction locale accélérée, ou réaction hâtive, et ont essayé de les utiliser comme une réaction diagnostique. Il y a spécialement deux groupes d'individus qui en l'occurrence ont intéressé USTVEDT:

1) Les personnes qui sont infectées de bactéries tuberculeuses mais qui pour une raison quelconque ne montrent pas de sensi-

bilité aiguë à la tuberculine. Tous ceux qui se sont occupés de vaccination BCG doivent avoir rencontré des cas qui, malgré des vaccinations BCG répétées, sont restés négatifs à la tuberculine pour 1 mg Mantoux. Les mêmes raisons doivent pouvoir expliquer l'existence d'individus négatifs dans un milieu tuberculeux. Une illustration de ce fait est une infirmière de l'Hôpital d'Enfants de Norrtull qui ne réagit pas positivement pour 1 mg Mantoux malgré des vaccinations BCG répétées et son contact journalier avec des cas de tuberculose.

2) Des personnes qui auparavant ont été positives et ont dans la suite réagi négativement. Par cela il ne faut pas entendre l'anergie temporaire en relation avec une autre maladie ou la réaction négative à la tuberculine dans certaines formes de la tuberculose. Il y a des cas prouvés qui ont traversé une tuberculose clinique qui ont été positifs mais dans la suite ont réagi négativement. Des exemples en sont donnés par H. KOCH (1927), ANZÉN (1929) (4) etc. USTVEDT signale une infirmière de 22 ans ayant un complexe primaire calcifié et un érythème noueux qui donnait une réaction négative à la tuberculine. Il y a de plus beaucoup de publications américaines d'exemples de calcification pulmonaires négatives à la tuberculine, quoique celles-ci doivent manquer de valeur en l'occurrence après que l'histoplasmose est maintenant connue. Chez nous, où des cas d'histoplasmose n'ont pas encore été décrit, G. OLSEN-BOJE (5) a examiné 206 cas de calcification pulmonaire et n'y a découvert qu'un cas insensible à la tuberculine.

Comment expliquer que dans de tels cas où il y a infection certaine la sensibilité à la tuberculine disparaisse? Ici nous entrons dans la question discutée de savoir si la réaction à la tuberculine s'éteint en même temps que l'infection tuberculeuse guérit définitivement. Beaucoup d'auteurs considèrent que tel est le cas. En faveur de cette opinion parle par exemple le cas de TERPLAN (6) qui indubitablement a été réinfecté et montré alors un nouveau complexe primaire comme s'il s'était agi d'une première infection, ou les examens de FELDMANN et BAGGENSTOSS (7) de 68 individus qui sont morts d'une autre cause que la tuberculose.

A l'émulsion du complexe primaire calcifié ils ont trouvé dans un seul cas des bactéries tuberculeuses. Ceci parle en faveur de ce que dans le complexe primaire calcifié il n'y a généralement pas de bactéries vivantes, mais n'exclut pas que des foyers d'ensemencement miliaire restent dans d'autres parties de l'organisme. Aussi en cette occurrence il y a lieu de considérer l'histoplasmose.

Il y a donc ici une possibilité d'expliquer le changement dans la sensibilité à la tuberculine: l'infection est guérie. Mais quel rapport y a-t'il entre la sensibilité à la tuberculine et l'immunité? A juger d'après les cas où la réinfection a montré un complexe primaire typique il semble que les deux facteurs doivent être adjoints. Cependant si nous allons aux examens de BIRKHAUG (8) nous voyons que des cobayes vaccinés par le BCG, sensibles à la tuberculine, peuvent être désensibilisés avec des doses croissantes de tuberculine de manière à ce que la sensibilité à la tuberculine disparaît. Il n'y a pas de raison de supposer que pour cette raison l'immunité disparaîtrait. En d'autres termes la sensibilité à la tuberculine et l'immunité ont ici été disjointes.

Nous avons donc deux possibilités d'expliquer la disparition de la sensibilité à la tuberculine chez les individus qui ont été atteints d'une infection tuberculeuse: soit une guérison définitive du processus tuberculeux, soit une sensibilité perdue malgré la persistance de l'infection.

Dans les ouvrages on décrit des renversements de la réaction à la tuberculine au négatif, là où la cause ne semble pas être une de celles signalées, mais peut s'expliquer par le fait qu'une réaction antérieure comprise comme positive peut avoir été non-spécifique. A l'injection sous-cutanée d'un mg de bouillon de glycérine à 53 patients, USTVEDT (3) a trouvé que 2 d'entre eux après 72 heures montraient une infiltration et une rougeur allant jusqu'à 10×10 mm. Si ces patients avaient été négatifs à la tuberculine et si l'on avait employé de la tuberculine au lieu de glycérine ils auraient erronément été considérés comme positifs. Avec la sensibilité à la tuberculine on doit compter sur une erreur de jugement qui dans certains cas peut avoir des conséquences considérables. Si donc un individu antérieurement sensible à la tuberculine perd sa sensibilité, il n'est pas nécessaire

qu'il s'agisse d'un renversement, car la première réaction peut avoir été non-spécifique.

THORKILDSEN et RINVIK (10, 11) montrent que des individus infectés artificiellement avec des germes tuberculeux de peu de virulence (BCG) ont aussi reçu la faculté de réagir couramment d'une autre manière lors d'une réinfection que des personnes qui n'ont pas été infectées auparavant. Ceci s'entend aussi pour des personnes qui, malgré la première infection, n'ont pas montré de sensibilité à la tuberculine. Pour cela on a pensé à la possibilité à l'aide de la réaction accélérée de pouvoir juger si un individu auparavant vacciné, qui malgré la vaccination n'est pas devenu sensible à la tuberculine, montre une modification des conditions de réaction des tissus, qui pourrait porter à croire à l'immunité. De la même manière on pourrait avec la réaction en question discerner le très petit nombre de personnes qui, malgré une infection de germes virulents, ne deviennent pas sensibles à la tuberculine. De plus on pourrait faire une distinction entre les réactions à la tuberculine spécifiques et non-spécifiques.

Lors des vaccinations en masse opérées ces derniers temps par les soins de l'UNICEF dans différents pays, la réaction locale, entre autres, a été étudiée. Ce matériel est référé dans la publication «The International Tuberculosis Campaign» (2). On a observé la réaction hâtive accélérée dans une assez grande extension. Dans un cas décrit par ORDELL, vacciné par erreur malgré la sensibilité à la tuberculine, il y a eu, comme attendu, une nécrose et ulcération: un phénomène de Koch.

Méthode

Il serait naturellement plein de risques lors de l'application du vaccin BCG en vue d'un but diagnostique d'employer la méthode intracutanée WALLGREN utilisée en Suède (12). USTVEDT et AANONSEN, suivant le modèle des méthodes multi-punctuaires de BIRKHAUG et ROSENTHAL à la vaccination BCG, ont appliqué le vaccin BCG sur la peau. Le vaccin dit ROSENTHAL, avec une concentration de 20 mg de bactéries par ml, préparé par le Dr. ANDERS WASSÉN de Gothembourg, a été employé. Avec deux aiguil-

les de gramophone fixées à deux centimètres de distance dans un manche on piqua deux gouttes de vaccin Rosenthal qui était placé sur la peau lavée.

A un examen de la réaction, qu'USTVEDT et AANONSEN appellent «réaction diagnostique BCG», nous avons à l'Hôpital de Norrtull appliqué une ou deux gouttes de vaccin Rosenthal sur la partie extérieure de la hanche droite et piqué ces gouttes dans l'épiderme avec une aiguille à injections ordinaire stérilisée de très fin calibre. Comme contrôle on a fait une piqûre semblable sans vaccin. La réaction diagnostique a été lue après 3 et 6 jours, le diamètre de la rougeur et de l'infiltration ont été données en mm, et on a annoté l'apparition de la petite papule décrite par USTVEDT. En même temps l'individu a été soumis à l'examen par tuberculine jusqu'à 1 mg Mantoux (Alttuberkulin). Par réaction négative à la tuberculine nous entendons ici toute réaction Mantoux à 1 mg d'alttuberkulin, où l'infiltration et la rougeur n'atteint pas 10×10 mm après 72 heures.

Matériel

L'examen a comporté des enfants entre 1 mois et 16 ans qui sont soignés à l'Hôpital d'Enfants de Norrtull ou ont été examinés dans sa polyclinique de BCG. Ils ont été divisés suivant les 3 groupes que voici:

- 1) enfants hospitalisés avec tuberculose primaire active bien caractérisée..... 69
- 2) enfants venus à la polyclinique Calmette pour vaccination BCG et se sont alors montrés négatifs à la tuberculine 104
- 3) enfants vaccinés par le BCG et revenus pour contrôle après la vaccination 262

Resultat

1) Patients avec tuberculose active bien caractérisée

Pour étudier l'aspect et le développement de la réaction diagnostique BCG chez des enfants de réaction tuberculinique posi-

tive certaine, 69 enfants hospitalisés avec tuberculose active ont été examinés. La réaction a été lue chaque jour pendant les deux premières semaines. Tous les 69 cas ont montré une réaction avec rougeur et infiltration de 2×2 mm ou plus de diamètre du 3^{ème} au 8^{ème} jour. Dans un petit nombre de cas la réaction était déjà disparue après le 7^{ème} jour. La plus grande réaction mesurée a été de 16 mm de diamètre. Quelques réactions isolées ont montré une ulcération centrale qui a duré jusqu'à 3 semaines et a guéri ensuite. On n'a pas observé de gonflement des ganglions lymphatiques ou autres complications. Dans 8 cas, au 6^{ème} jour, la réaction n'a pas été plus grande que 2×2 mm, mais dans aucun cas la papule typique décrite par USTVEDT (3) n'a manqué, et une telle réaction est, à notre avis, facile à distinguer d'une réaction entièrement négative (la marque après la piqure de contrôle). La grandeur moyenne de la réaction était au 3^{ème} jour de 5,7 mm et au 6^{ème} de 5,8 mm.

2) Examens avant la vaccination BCG

Il s'est agi d'enfants venus à la polyclinique de BCG pour être vaccinés par le BCG. En même temps que l'essai cutané avec la Néotuberculine, la réaction diagnostique BCG fut opérée. Après 72 heures ces deux réactions ont été lues et l'enfant a été éprouvé avec 1 mg Mantoux, réaction qui a été lue après encore 72 heures en même temps qu'une nouvelle lecture de la réaction diagnostique BCG.

Tableau.

Examens à la tuberculine avant la vaccination BCG:

Nombre de négatifs à la tuberculine	104
Réaction diagnostique BCG négatifs 6 ^{ème} jour	104
» » » » 3 ^{ème} »	97
» » » » 2×2 mm. ou plus	
* grande 3 ^{ème} jour	7

Les 7 cas qui avaient montré une réaction de 2×2 mm ou plus grande le 3^{ème} jour ont été tous complètement négatifs le 6^{ème}

jour. Ils ont été traduits comme réactions non-spécifiques et illustrent l'opinion d'USTVEDT que la réaction doit être lue plus tard que le 3^{ième} jour.

3) Examen des enfants vaccinés par le BCG

Lorsque les enfants ont été vaccinés par le BCG, ils reviennent pour réexamen après 2—3 mois. Ils ont été traités avec 1 mg Mantoux. En même temps il a été opéré à la réaction diagnostique a été lue le 3^{ième} et le 6^{ième} jour. Le résultat est consigné dans le tableau suivant:

Réexamen des enfants vaccinés BCG:

	3 ^{ième} jour	6 ^{ième} jour
Nombre examiné.....	262	262
Tuberc. posit., réaction BCG 2 × 2 mm ou plus grande.....	246	249
Tuberc. négat., réaction BCG négative	10	10
» » » » 2 × 2 mm ou plus grande.....	3	3
Tuberc. posit., réaction BCG négative.....	3	0

Comme il ressort du tableau dans trois cas de réaction positive à la tuberculine la réaction diagnostique BCG a été insuffisamment grande le 3^{ième} jour, mais dans tous cas elle a augmenté et est devenue positive (2 × 2 mm ou plus) le 6^{ième} jour. La lecture de la réaction doit donc avoir lieu environ ce jour-là comme USTVEDT l'a préconisé. Le 6^{ième} jour tous les cas réagissant positivement à la tuberculine ont aussi montré une réaction diagnostique BCG avec 2 × 2 mm ou plus, mais de plus il y a 3 cas de réaction négative à la tuberculine qui ont montré une réaction diagnostique BCG de 2 × 2 mm ou plus. On peut probablement supposer que ces 3 cas, bien qu'ils ne soient pas sensibles à la tuberculine, par la vaccination ont obtenu une modification de mode de réaction des tissus résultant en une réaction hâtive accélérée.

Nous nous étions aussi attendus à ce que les 10 enfants vacci-

nés BCG qui n'étaient pas sensibles à la tuberculine auraient malgré cela une réaction hâtive. Tel ne fut cependant pas le cas. De la même manière on a examiné des enfants en bas-âge de milieu tuberculeux qui sont hospitalisés dans l'attente de constater la sensibilité à la tuberculine après la vaccination par le BCG. Ceux-ci non plus ne montrèrent la réaction hâtive qu'après être devenus sensibles à la tuberculine. Trois enfants eurent une réaction hâtive positive bien qu'ils ne fussent pas sensibles à la tuberculine après la vaccination BCG, tandis que 10 enfants étaient négatifs aussi bien à la tuberculine qu'à la réaction BCG. Peut-être que la tuberculine BCG (13) aurait dans ces cas donné encore des réactions positives.

Au point de vue pratique la révaccination semble être à préconiser lorsque la sensibilité est si faible que l'examen à la tuberculine ne devient pas positif.

Discussion

A notre avis une réaction BCG de 2×2 mm de diamètre ou plus et avec une papule distincte, malgré sa petitesse, est facile à différencier d'une réaction entièrement négative et doit être considérée comme positive. Dans notre matériel elle n'a pas donné de complications mais chez des patients avec une tuberculose primaire active elle a laissé dans quelques cas sporadiques une petite ulcération superficielle qui s'est guérie après 2 à 3 semaines. Elle a de plus été négative chez les enfants négatifs à la tuberculine et non vaccinés par le BCG, positive chez les enfants positifs à la tuberculine et avec une tuberculose primaire bien établie, et aussi positive après vaccination par le BCG dans tous les cas où là aussi la réaction à la tuberculine a été positive. En outre la réaction diagnostique BCG a été positive dans 3 cas encore (1,1 %) chez des enfants vaccinés par le BCG là ou 1 mg Mantoux avait été négatif. On peut discuter la signification de ce fait. Peut-être est-il l'expression d'une modification des tissus dans l'organisme après la vaccination par le BCG qui n'a pas donné source à une sensibilité à la tuberculine.

Résumé

Les auteurs ont étudié la littérature résumée au sujet du phénomène de Koch dans la forme où Ustvedt l'appelle la réaction diagnostique BCG. Des problèmes théoriques ont été discutés en relation avec cette étude, ainsi que la technique de l'examen. Le matériel des auteurs a consisté en 69 enfants réagissant positivement à la tuberculine et atteints de tuberculose primaire active, tous positifs aussi avec la réaction diagnostique BCG. 104 cas négatifs à la tuberculine tous négatifs à la réaction diagnostique BCG, et 262 enfants vaccinés par le BCG, dont 246 positifs à la tuberculine et 249 positifs à la réaction diagnostique BCG. En dehors de l'intérêt théorique de cette réaction, l'attention est attirée aussi sur la possibilité de l'employer dans les cas où, malgré une infection tuberculeuse probable, les patients ne sont pas sensibles à la tuberculine, et peut-être aussi, suivant Ustvedt, pour différencier les réactions à la tuberculine dites fausses des réactions spécifiques, bien que les auteurs n'aient constaté aucun cas de ce genre. La réaction pourrait aussi être utilisée comme contrôle des vaccinés par le BCG.

M. D'AVIGNON and S. NORSTEDT: *Diagnostic Reaction of BCG* (Ustvedt).

The authors have studied surveys of the literature on the subject of Koch's phenomenon, in the form described by Ustvedt as the diagnostic reaction of BCG. Theoretical problems are discussed in relation to this study, also the examination technique. The authors' material consisted of 69 children with positive reaction to tuberculin and suffering from active primary tuberculosis, thus all positive to the diagnostic reaction BCG, 104 cases negative to tuberculin and all negative to the diagnostic reaction BCG, and 262 children inoculated with BCG, of whom 246 were positive to tuberculin and 249 positive to the diagnostic reaction BCG. Besides the theoretical interest of this reaction, attention is drawn also to the possibility of utilising it also in cases where, despite a probable tuberculous infection, the patients are insensitive to tuberculin and perhaps also, according to Ustvedt, for differentiation of so-called false reactions to tuberculin from specific reactions, though the authors themselves have not observed any case of this kind. The reaction might also be utilised as control of persons inoculated with BCG.

M. D'AVIGNON und S. NORSTEDT: *Die diagnostische BCG-Reaktion* (Ustvedt).

Die Verfasser haben die zusammengefasste Literatur des Phenomens von Koch in der Form, in der Ustvedt sie die diagnostische Reaktion

BCG nennt, studiert. Theoretische Probleme im Zusammenhang mit dieser Studie und die Technik der Untersuchung sind diskutiert worden. Das Material der Verfasser bestand aus 69 Kindern, Fälle von primärer aktiver Tuberkulose, die auf Tuberkulin positiv reagiert haben und sämtlich auch mit der diagnostischen Reaktion BCG positiv waren; 104 tuberkulinnegative Kinder, sämtlich auch auf die diagnostische Reaktion BCG negative Fälle, sowie 262 BCG-geimpfte Kinder, von denen 246 für Tuberkulin und 249 für die diagnostische Reaktion BCG positiv waren. Ausser dem theoretischen Interesse dieser Reaktion wird die Aufmerksamkeit auch auf die Möglichkeit gerichtet, sie in den Fällen anzuwenden, in denen die Patienten trotz möglicher tuberkulöser Infektion für Tuberkulin nicht empfindlich sind, und vielleicht auch, nach Ustvedt, um die Reaktionen auf Tuberkulin zu differenzieren, die fälschlich spezifische Reaktionen genannt werden, obwohl die Verfasser keinen Fall dieser Art konstatiert haben. Die Reaktion kann auch als Kontrolle der BCG-Geimpften benutzt werden.

M. D'AVIGNON y S. NORSTEDT: *La reacción diagnóstica BCG* (Ustvedt).

Los autores han estudiado la literatura resumida respecto al fenómeno de Koch en la forma en la que Ustvedt la llama la reacción diagnóstica BCG. Los problemas teóricos han sido discutidos en relación con este estudio, así como la técnica del examen. El material de los autores ha consistido en 69 niños que han resistido positivamente la tuberculina y atacados de tuberculosis primaria activa, todos positivos también con la reacción diagnóstica BCG; 104 casos negativos a la tuberculina, todos negativos a la reacción diagnóstica BCG, y 262 niños vacunados BCG, de los cuales 246 positivos a la tuberculina y 249 positivos a la reacción diagnóstica BCG. Aparte del interés teórico de esta reacción, se ha dirigido la atención también sobre la posibilidad de emplearla en los casos donde, a pesar de una infección tuberculosa probable, los pacientes no son sensibles a la tuberculina y quizá también, según Ustvedt, para diferenciar las reacciones a la tuberculina llamadas falsas de las reacciones específicas, aunque los autores no habían comprobado ningún caso de este género. La reacción podría ser utilizada también como control de las vacunas por el BCG.

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5.12. 1950.

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BOOK REVIEW

The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. By LAWSON WILKINS, M. D. Price \$ 13. Charles C. Thomas, Publisher, Springfield, Illinois, U. S. A. 1950.

The rapid advancement of endocrinology in recent years is reflected in an increasing amount of published papers and new textbooks dedicated to the theoretical or clinical part of the physiology and pathology of the glands of internal secretion. There has, however, been a lack in this field felt by those interested in pediatric endocrinology. No comprehensive textbook on this subject has hitherto been published. The pediatrician with an interest in hormonal disorders has been often forced to troublesome search of original articles or referred to textbooks concerned mainly with adult endocrinology.

The newly published book of pediatric endocrinology, "The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence," by L. Wilkins, must for these reasons be said to supply a real need. This book is the more welcome as the author is well known both as a pediatrician and as an endocrinologist.

The first chapters of the book are dedicated to the influence of hormones on growth and development and to endocrine relationships. This part of the book contains a brief, remarkably clear survey of the modern conception of glandular physiology. The following chapters treat the methods of endocrine study. The clinical examination, including evaluation of the level of growth and development, and the values and limitations of laboratory tests are discussed. The main part of the book deals with the endocrine disorders of childhood with the exception of diabetes mellitus. The chapters have not strictly been arranged so that diseases of one particular gland are treated together. In several instances the author has dealt with symptom complexes, such as dwarfism or sexual infantilism, which from the didactical point of view seems to be preferable. In connection with each chapter is an atlas with short case notes, mostly from the author's own experience, photographs of outstanding quality, microphotographs, X-rays and schematic drawings. The chapters are concluded with a large bibliography. The last part of the book deals with congenital anomalies sometimes mistaken for endocrine disorders.

This book is written by an experienced teacher, a critical investigator and a good writer. The author's statement in the preface that, when choosing between conflicting hypotheses, he has been influenced by his own experience and preference, seems rather to be a guarantee that the opinions expressed are founded on a sound basis. The author's critical mind is reflected in his conservative attitude towards hormonal treatment.

The book is written for the clinician and ought to find its way into the library of pediatric clinics, but it can equally strongly be recommended to the pediatric practitioner with an interest in this special field of medicine.

C. G. Bergstrand

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FROM THE PEDIATRIC UNIVERSITY CLINIC OF THE MUNICIPAL HOSPITAL,
AARHUS, DENMARK. CHIEF: PROFESSOR BENT ANDERSEN, M.D.

Isolated Interstitial Myocarditis of Unknown Etiology

Three Cases in Infants

by

POUL BASTRUP-MADSEN

During recent years some cases of myocarditis of unknown etiology have been described in the literature. These cases have been published under various names, such as primary interstitial, idiopathic, or isolated myocarditis, or Fiedler's myocarditis, named after FIEDLER, who first described the condition (1899). The literature on this subject has been reviewed in detail by SAPHIR *et al.* (1942, 1944). In the Scandinavian literature one case occurring in an adult was reported by KJAERGAARD (1938).

"Isolated interstitial myocarditis" is generally defined as an inflammatory reaction within the myocardium, while the endocardium and pericardium are not involved; there are no demonstrable pathological changes which may explain the origin of the myocarditis. Histologically, the disease is chiefly characterized by infiltration of lymphocytes, leukocytes, eosinophilic cells, plasma cells, and large mononuclear cells (histiocytes?) in the interstitial tissue of the myocardium. Most commonly, diffuse cellular infiltration in the connective tissue of the myocardium is encountered, but occasionally extensive collections of cells of a more focal character may be seen. At the same time there may be some places in which the muscle cells have disintegrated. The parenchymatous damage is supposed to be secondary to the changes of the connective tissue and differs from the toxic primary hyaline parenchymatous degeneration which is seen in diphtheria and various intoxications (e. g., phosphorus). There are no specific inflammatory changes of the con-

nective tissue as in rheumatic fever or tuberculosis. Thus, "isolated interstitial myocarditis" does not differ histologically from the simple unspecific myocarditis which may accompany any of the known infectious diseases.

Clinically, the disease is manifested by progressive congestive heart failure with dyspnea, cyanosis, tachycardia, enlarged liver, low blood pressure, cardiac enlargement and electrocardiographic changes. Occasionally, these symptoms are accompanied by fever. In many cases the diagnosis has not been established until post mortem; in some instances only after microscopic examination of the heart because its gross appearance seemed normal. In all the cases reported in the literature the disease has terminated fatally, most frequently shortly after the onset; in some cases it has resulted in sudden unexpected death. It seems to be most frequent in adults.—As only a comparatively small number of cases of Fiedler's myocarditis in children have been published (GREENEBAUM *et al.*, 1941; HOUSE, 1948; JONES *et al.*, 1948; LINDBERG, 1938; MASLOW *et al.*, 1933; SAPHIR *et al.*, 1944), three cases of the disease in infants will be reported below.

Case 1. (No. 454/46.) The patient was a one year old girl, the second of two children of healthy parents. The mother had been well during the pregnancy. Full term at birth, weight 3 000 g. The child had developed normally. At nine months she had fever (39°) for two or three days without any known cause. At that time she was rather weak and had refused her feedings, but she recovered quickly. Otherwise she had always been in good health.

During the three days previous to admission she had been very quiet, whimpered a little, refused to eat, and drank little. During this period the child had had a few sudden attacks of extreme weakness and pallor with cyanotic lips and dull eyes. She had vomited once or twice daily. The mother had noticed that the patient had a very rapid pulse during the disease. The temperature had been normal on several occasions. There was no history of cough, coryza, discharge from the ears or diarrhea; but the urine had been somewhat scanty.

On admission the girl was extremely weak and pale with cyanotic lips and dyspnea; temperature 37°; pulse rate 120—130, but regular. She was not dehydrated. The fauces were normal, without redness or swelling. Auscultation revealed that the cardiac borders were at the third rib and the middle of the sternum; the apex was felt in the fifth

intercostal space in the mid-clavicular line. The heart sounds were somewhat dull, but no murmurs were audible. At the apex a distinct gallop rhythm was heard. The abdomen was soft; the liver was felt to be definitely enlarged with a firm, blunt lower border.

The patient was treated with oxygen and sympatol, but the following day she was still very weak, somewhat restless, and more cyanotic than on admission. The liver had further increased in size, now extending to 5 cm below the costal margin. The pulse rate was 184. The temperature was still normal, but in the evening it rose to 38.5°. Her condition became critical; she was very cyanotic and restless, with grunting respiration. The pulse was sometimes imperceptible. She died shortly afterwards.

At autopsy a hypertrophied and dilated heart with normal endo- and pericardium was found; also hydrothorax, congestion of the liver, lungs, spleen, and kidneys, but no evidence of pneumonia. At the histologic examination the pathologist (W. Munck, M.D.) found very pronounced inflammatory changes of the heart, with edema, hyperemia, and cellular infiltrations in the connective tissue. In many places there were considerable infiltrations of lymphocytes, plasma cells, and polymorphonuclear leukocytes. The infiltrations often split the muscular fibres from each other, and there was some degeneration of the fibres with swelling, loss of striation, and sometimes destruction. The lungs showed congestion and edema, but no pneumonia. Diagnosis: Acute myocarditis.

Case 2. (No. 33/49.) The patient was a 17 day old boy, the first child of healthy parents. The mother had been well during the pregnancy. The infant was born two weeks before the expected time, but the birth weight was 3 100 g. The delivery had been normal; the neonatal course had been good, without any symptoms of disease.

During the five days previous to admission the infant had been very weak and pale, had whimpered and lost his appetite; the respiration was grunting. He had had a slight coryza and had coughed a little during the last two days. On the day of admission he began to get cyanotic around the mouth and on the nose. The temperature had been normal on two or three occasions.

On admission he was very weak, with rapid, shallow, and grunting respiration. He did not cry, but only whimpered faintly and was rather cyanotic. The temperature was 38°. The fauces were normal, without swelling or redness. Auscultation of the heart did not reveal anything abnormal. Fine moist râles were heard over the lungs. The liver was palpable 4 cm below the costal margin. Examination of the spinal fluid did not disclose pathologic features. Electrocardiography showed a cardiac action of 150-160 beats per minute, sinus rhythm, a slight deviation of the axis to the right; the T waves were low, almost isoelectric in all three leads. Hemoglobin 105 per cent.

He was at once given oxygen and the cyanosis disappeared. But when the oxygen was withdrawn, the cyanosis quickly reappeared. The condition remained unchanged for the next 48 hours. He fed poorly and did not pass much urine. For this reason saline was given subcutaneously, but it was poorly resorbed. The temperature remained normal throughout. On the second day after admission a severe exacerbation of the condition suddenly occurred; he became very dyspneic and cyanotic, even when oxygen was administered. Injections of lobeline and nikethamide were given without effect, and the infant died shortly afterwards.

The autopsy revealed an enlarged heart. The ductus arteriosus was still patent, but otherwise no malformations were found. The myocardium was dark and swollen; the cut surface was mottled, with numerous greyish-yellow areas. In several places there was extravasated blood. The appearance of the endo- and pericardium was normal. Extensive atelectases but no pneumonias were seen. Congestion of the liver was observed. Other organs were normal.

At the histologic examination the pathologists W. Munck, and J. Dalgaard found considerable pathologic changes in the heart, viz., hyperemia, degeneration of muscle fibres, and cellular infiltration in the connective tissue. The vascular dilatation involved both veins and capillaries, which were often full of closely packed red blood cells. The muscle fibres were as a rule of normal appearance with distinct striation, but in places they showed some degeneration, with a decrease in the staining capacity and without visible striation. In some areas the nuclei had disappeared. The cellular infiltrations were partly focal in character and partly more diffuse and consisted predominantly of lymphocytes, but also some plasma cells, eosinophilic leukocytes and large phagocytes with scanty amounts of chromatin in the nuclei were seen. There was no fibrosis. *The pulmonary tissue* contained less air than normal; the capillaries were dilated and filled with blood; the alveoli were filled with edematous fluid. There was no evidence of pneumonia. Diagnosis: Acute myocarditis.

In both these cases there were typical symptoms of cardiac insufficiency: poor general condition, dyspnea, cyanosis, tachycardia, and enlarged liver. The clinical examination did not reveal any signs of infection which might account for the myocarditis. Except for the heart disease, the autopsies disclosed only such changes as could be explained by the cardiac insufficiency. Microscopically, interstitial inflammatory changes in the myocardium and only a few scattered areas with degeneration of the muscle fibres were found. According to the definition men-

tioned previously, the diagnosis must in both cases be isolated interstitial myocarditis or Fiedler's myocarditis.

Case 3. (No. 415/46.) The patient was a 17 month old girl of healthy parents; she was the last of six siblings, born at term, birth weight 4 000 g. She had developed normally. She had had measles at 12 months and rubella at 15 months, but had otherwise been in good health. During the two months prior to admission she had been somewhat tired and weak and had had a poor appetite. Yet she had been up and about and been able to play until a week before admission.

During the week previous to admission she had had attacks of dyspnea, accompanied by cyanosis of cheeks and lips. She vomited occasionally during the attacks, which lasted from 10 to 15 minutes. During this period she was very tired and lax and had to remain in bed. Mostly she lay very quiet, but sometimes she became restless and whimpered, putting her hands on her stomach. The temperature had been normal all the time.

On admission she was extremely weak; she cried and was very cyanotic, especially on the cheeks and lips. Her skin was of a mottled appearance. She was dyspneic with a respiratory rate of 64, temperature 36°.3 C. Her development corresponded to her age. The fauces were normal without redness or swelling. Auscultation of heart and lungs showed nothing abnormal. The liver was not palpable. The limbs were normal without edemas.

After admission she was constantly slightly cyanotic. She was given 1.5 mg ethylmorphine and slept well at night. The next day the condition was unchanged; she was cyanotic and listless; yet now and again she sat up in bed; the appetite was poor. At 5.30 p. m. she had been attended to and nothing particular had been noted. The cyanosis was unchanged. At the evening round ten minutes later she was found dead. A lumbar puncture was done immediately and a clear colourless spinal fluid with 10/3 cells per c.mm was found.

Autopsy disclosed a markedly enlarged heart. The enlargement involved all parts of the heart, but predominantly both auricles and the left ventricle, the wall of the latter measuring 10 mm. The myocardium appeared normal on the cut surface. Ostia and valves were normal. A patent foramen ovale was seen, 0.5 cm in diameter. The appearance of the endo- and pericardium was normal. The coronary vessels were of normal size. The liver was enlarged, of increased consistency, and with a nutmeg pattern on the cut surface. In the peritoneal cavity 125 ml of a clear, yellow fluid was found. The diagnosis on autopsy was: Cardiac disease, patent foramen ovale, congestion of the liver. Unfortunately, by a mistake no sections were selected for microscopy.

As in the two first cases, the picture was dominated by cardiac insufficiency. At autopsy an enlarged heart with thickened walls was found. There were signs of congestion of the liver. The pathological findings suggested myocarditis. As in the first two cases it must then have been an isolated myocarditis as there were no infectious foci which could account for the disease. As by a mistake no microscopic examination of the heart was carried out, one must, of course, be a little reserved about the definite diagnosis. There were no congenital or acquired malformations which might explain the cardiac hypertrophy. The patent foramen ovale cannot either explain the cardiac hypertrophy or insufficiency. In addition to myocarditis, the only diagnosis which must be considered is one of the rare idiopathic congenital cardiac hypertrophy.

The diagnosis of myocarditis may be difficult to establish in an infant. In the three cases reported here the patients showed symptoms on admission which must be attributed to cardiac insufficiency. They were extremely weak and had pronounced dyspnea, cyanosis, and tachycardia, but their condition may be difficult to differentiate from poor general condition due to other causes. Pneumonia must be supposed to be the most frequent cause of this picture with extreme weakness, dyspnea, cyanosis, and tachycardia in an infant, but miliary tuberculosis must also be considered. A picture such as the one described here may also be seen in meningitis, especially if accompanied by meningococcal sepsis,—in fact sepsis of any type. A poor general condition of sudden onset such as this may also be seen in subarachnoid hemorrhage. A similar clinical picture may sometimes be encountered in cases in which no definite diagnosis can be established. If—in analogy with the findings in the first two cases reported—enlargement of the liver can be demonstrated, this may be a clue as to the proper diagnosis. However, these cases of rapidly progressing acute myocarditis may not always run a sufficiently long course to manifest themselves in a clinically demonstrable “back pressure.” The electrocardiogram will rarely show anything but tachycardia. Low or inverted T waves in an infant may suggest myocardial damage. A roentgen ex-

amination may show an enlarged heart, but often the roentgenographic interpretation of the conditions found in an infant presents difficulties.

The etiology of isolated myocarditis is unknown. It may be reasonable to suppose that it is an infectious disease since pathologically it does not differ from the type of myocarditis which may occur as a complication in any of the known infections. But whether "isolated interstitial myocarditis" is produced by a specific pathogenic micro-organism or is a manifestation of various infections is unknown. As pathologically there is no evidence that isolated myocarditis is a disease *sui generis*, it seems reasonable to use the term "isolated interstitial myocarditis of unknown etiology." In my opinion, the term "Fiedler's myocarditis" may give a false indication of a known etiology and a well-defined disease entity. But nevertheless it is, of course, important to be aware that a myocarditis may be encountered even though the patient does not suffer from rheumatic fever, diphtheria, tonsillitis or pneumonia.

As in any other type of acute myocarditis the most important factor in the treatment is the institution of undisturbed bed rest. Acutely ill patients may benefit from administration of oxygen. Digitalis therapy has been recommended, but is rarely of any appreciable benefit in acute myocarditis, and sometimes it may even aggravate the condition of the patient. The most essential feature in the treatment of an acute myocarditis must always be to combat the underlying infection, but as we do not know the cause of isolated interstitial myocarditis, we are rather powerless in the treatment of the disease.

Summary

Three cases of acute interstitial myocarditis of unknown etiology in infants are reported. In all three cases the disease manifested itself by progressive cardiac insufficiency with poor general condition, dyspnea, cyanosis, tachycardia, and an enlarged liver. The disease terminated fatally in the course of 4—8 days. In all three cases autopsy revealed an enlarged soft and flabby heart and signs of congestive heart failure. In the first two cases microscopy showed diffuse interstitial

cellular infiltrations in the myocardium. Microscopic examination was not made in the third case. No foci which might be regarded as the cause of the myocarditis were found.

P. BASTRUP-MADSEN: *Myocardite aiguë interstitielle d'étiologie inconnue.*

Il est rapporté 3 cas de myocardite aiguë interstitielle chez l'enfant d'étiologie inconnue.

Dans les 3 cas, la maladie se manifesta par une insuffisance cardiaque progressive avec atteinte de l'état général, dyspnée, cyanose, tachycardie et hépato-mégalie. Le décès survint après un délai variant de 4—8 jours.

L'autopsie révéla dans les 3 cas une hypertrophie molle et flasque du cœur et des signes de congestion cardiaque. L'examen microscopique montra dans les deux premiers cas des infiltrations cellulaires interstitielles du myocarde. L'examen microscopique ne fut pas pratiqué dans le 3^e cas. Aucun foyer pouvant être considéré comme le point de départ de la myocardite ne fut trouvé.

P. BASTRUP-MADSEN: *Akute interstitielle Myocarditis unbekannter Ätiologie.*

3 Fälle von akuter interstitieller Myocarditis unbekannter Ätiologie bei Säuglingen werden berichtet. In allen 3 Fällen manifestierte sich die Erkrankung durch zunehmende Herzinsuffizienz mit schlechtem Allgemeinzustand, Dyspnoe, Cyanosis, Tachycardie und Lebervergrößerung. Die Krankheit endete tödlich im Laufe von 4—8 Tagen.

In allen 3 Fällen fand sich bei der Autopsie ein vergrößertes, weiches und schlaffes Herz mit Zeichen von kongestivem Herzfehler. In den ersten 2 Fällen zeigte die mikroskopische Untersuchung diffuse, interstitielle Zellinfiltrationen im Myokard. Im 3. Fall wurde keine histologische Untersuchung gemacht. Irgendwelche Herde, die als Ursache der Myokarditis hätten angesehen werden können, wurden nicht gefunden.

P. BASTRUP-MADSEN: *Miocarditis intersticial aguda de etiología desconocida.*

Se relatan tres casos de miocarditis intersticial aguda de etiología desconocida en tres niños. En los tres casos la enfermedad se manifestó por insuficiencia cardíaca progresiva con mal estado general, disnea, cianosis, taquicardia y dilatación del hígado. La enfermedad terminó fatalmente en el curso de 4 a 8 días. En los tres casos la autopsia reveló un corazón dilatado, débil y sin vigor, y signos de parálisis congestiva del corazón. En los dos primeros casos el microscopio mostró

infiltraciones celulares intersticiales difusas en el miocardio. En el tercer caso no se ha hecho examen al microscopio. No se han encontrado focos que pudieran ser considerados como la causa de la enfermedad.

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FROM THE UNIVERSITY CHILDREN'S CLINIC, HELSINKI.
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On the Use of Mare's Milk in Infant Feeding

by

H. KALLIALA, ESTER SELESTE and NIILLO HALLMAN

During the last century ass's milk has along with cow's milk and different cow's milk preparations been widely used instead of human milk (especially in France and Germany). Its composition resembles in many respects that of breast milk. It is, however, difficult to obtain and therefore it is scarcely used anywhere nowadays. Recently FREUDENBERG (1946) has drawn attention to mare's milk, the composition of which is very similar to ass's milk and human milk. During the years 1945 and 1946 he has used 471.8 litres of mare's milk, which was collected from different farms, for infant feeding. As far as we know this is the only paper on infant feeding with mare's milk. It has been used occasionally in Iceland and seems to be especially suitable for pylorospasm (THORODDSEN).

In the summer of 1949 Mr. AALTO, Director of the State Stud, Ypäjä, Finland, offered to send us a daily supply of mare's milk. We therefore had a chance of obtaining experience with the use of this milk in infant feeding together with the possibility of carrying out certain investigations on it. We want to express to him our most sincere thanks for his valuable help.—The mare's milk proved especially useful during the summer when the supply of breast milk was at its lowest and the need of it high during the enteritis epidemics.

The Supply and Handling of the Mare's Milk

After some preliminary experiments the Children's Clinic has used during June–November 1949 from 10 to 20 litres of mare's

milk daily as a supplement to breast milk, when the supply of the latter was insufficient. Altogether the amount used is a little over 2 000 litres. It looks more transparent than cow's milk but more opaque than human milk.

The hygienic conditions of the Ypäjä Stud equal those of a fairly clean cow-house. The milking has been performed by the stud workers into special thoroughly cleaned cans. The milk has been cooled at once and during the hot season it was sent to the hospital in cooled pails. In the hospital it has been immediately pasteurized by keeping it at a temperature of 62° C for 20 minutes. According to FREUDENBERG (1946) even a short boiling would cause considerable flocculation of the albumin and so this method is not suitable.

The number of mares milked has varied from two to eleven and in most cases the milking could be performed without much difficulty. During the lactation period the daily amount obtained by the colt is from 10 to 30 litres. The amount of a single feed is, however, small, the colt compensating for this by feeding frequently, almost hourly during day-time. The colt must be separated from its mother for two hours before milking and even so the amount obtained is small, from $\frac{1}{2}$ to $1\frac{1}{2}$ litres. After weaning, the amount that can be obtained decreases rapidly which may depend partly on the milking being performed only every four hours for practical reasons. During the first days a mare would give from 5 to 6 litres daily but after a week only from 1 to $1\frac{1}{2}$ litres. The output might be increased by milking the mares more often, but this has not been feasible. It is possible that by this method mare's milk might be obtained for a long period after the weaning of the colt.

Chemical Analysis

As shown in table I, the values obtained by us correspond with those obtained by earlier authors. The protein content of mare's milk is low as compared with that of cow's milk but it still contains about $\frac{1}{2}$ % more than human milk and also more than the "half-milk" mixture from cow's milk commonly used for infants during the first three months of life. Qualitatively it resembles

Table I.
Composition of milk in %.

Substances analyzed	Mare's milk					Ass's milk (Raudnitz)	Human milk (Brock)	Cow's milk (Brock)
	Own results			Freuden- berg	König (Abder- halden)			
	Number of determi- nations	Limit values	Mathemat- ical average					
Water content	—	—	—	—	—	90.12	—	—
Total protein ¹	16	1.65-2.22	1.96	1.91	2.11	1.8	1.40	3.50
Casein ²	5	0.64-0.76	0.70	0.58	—	0.8	0.65	2.50
Other proteins ²	5	1.01-1.21	1.11	1.23	—	1.0	0.53	0.48
Sugar ²	6	5.98-6.05	6.03	7.43	6.67	6.0	7.00	4.50
Fat ²	30	0.30-2.40	0.71	1.1	0.88	1.3	4.00	3.50
Cal./100 gm.	—	—	38.5	47.2	44.6	45.0	70.0	66.0
Ash	5	0.33-0.43	0.37	—	0.38	0.47	0.30	0.75
Potassium ⁶	9	0.043-0.057	0.049	—	(0.083)	0.070	0.053	0.160
Sodium ⁵	9	0.013-0.015	0.014	—	(0.0074)	0.0024	0.014	0.045
Calcium ⁶	9	0.101-0.142	0.120	0.081	(0.080)	0.076	0.028	0.128
Iron ⁷	11	0.00053- 0.0014	0.00095	—	(0.0014)	0.0007	0.00015	0.00018
Chlor ⁸	9	0.041-0.048	0.044	—	(0.03)	0.031	0.030	0.097
Phosphorus ⁸	9	0.044-0.071	0.053	0.041	(0.056)	0.058	0.015	0.098

¹ Kjeldal, ² Isoelectric flocculation.

³ Hagedorn-Jensen.

⁴ Aether extraction.

⁵ Whitehorn.

⁶ Kramer-Tisdall.

⁷ Sandell: Colorimetric determinations of traces of metals.

⁸ Bodansky.

⁹ Flanephonometer.

human milk in that more than half of its protein is easily digestible lactalbumin.

The lactose content is high; in our samples it was a little lower than stated in some earlier papers. The fat content is very low and rather variable but the fat resembles qualitatively that of human milk as both contain a high percentage of unsaturated fatty acids (FREUDENBERG 1948). The content of fat-soluble vitamins is accordingly also low; on the other hand the content of the vitamins B₁, B₂ and B₆ is sufficient when judged by accepted standards and that of vitamin C even in excess (FREUDENBERG). As a result of the low fat content there is a low caloric value, which can be overcome by adding other easily obtainable food stuffs.

The mineral content is on the same level as in human milk, i.e., about one half the amount found in cow's milk. However, the amount of calcium and phosphorus, especially the former, is relatively higher and in our samples was only a little lower than in cow's milk.

Our results disagree slightly with those of ABDERHALDEN. The iron content of mare's milk is clearly higher than of human and cow's milk. The values are nearly the same as those found in ass's milk (RAUDNITZ).

Hygienic Aspects of Mare's Milk

In his paper FREUDENBERG assumes that mare's milk would be cleaner than cow's milk, as the horse is a "cleaner" animal than the cow (dry stools). On the other hand, the hygienic requirements for a cow-house are greater than for a stable.

As far as we know no bacteriological work on mare's milk has been published.

We have performed a simple culture on a blood agar plate from samples.

Sample 1: numerous gram—cocci and gram + cocci in groups and gram—bacilli (coli group).

Sample 2: numerous gram—and gram + cocci and gram—bacilli.

Sample 3: numerous gram—bacilli and cocci.

Sample 4: numerous gram + and gram—cocci and gram + bacilli. Some gram + cocci (staphylococcus aureus non-haemol.).

Sample 5: numerous gram + large bacilli, gram—cocci and gram + cocci.

As much work has been done on the bacteria of cow's and human milk we only refer here to the literature. According to our rough analysis the bacterial flora of mare's milk corresponds with that of cow's milk (THOMÉ).

It is an international custom to classify milk according to the results of the reductase test. A certain amount of methylene blue is added to the milk and it is allowed to stand at a temperature of 38° C until the blue colour disappears. According to BARTHEL the reductase test principally shows the keeping properties of the milk and not directly the number of bacteria present, although the speed of disappearance of the blue colour is usually proportional to the bacterial count of the milk, which can be seen from the classification principles in dairy practice (THOMÉ).

First class milk: blue colour remains for more than 5 1/2 hours, bact. count 750 000/ml.

Second class milk: blue colour remains for from 3 to 5 1/2 hours, bact. count < 5 million/ml.

Third class milk: blue colour remains from 20 min. to 3 hours, bact. count 4 to 20 million/ml.

Fourth class milk: blue colour remains for less than 20 min., bact. count over 20 mill./ml.

We have compared some samples of human, cow's and mare's milk in the reductose test:

	Human milk Colour remains	Cow's milk Colour remains	Mare's milk Colour remains
1.	> 5 1/2 hours	> 5 1/2 hours	4 1/2 hours
2.	> 24 "	> 24 "	6 "
3.	24 "	24 "	3 1/2 "
4.	24 "	24 "	> 5 1/2 "
5.	24 "		> 5 1/2 "
6.	24 "		

Whereas all samples of human and cow's milk kept very well, two of the five samples of mare's milk were second class. This may not be a sign of lower keeping properties of the mare's milk

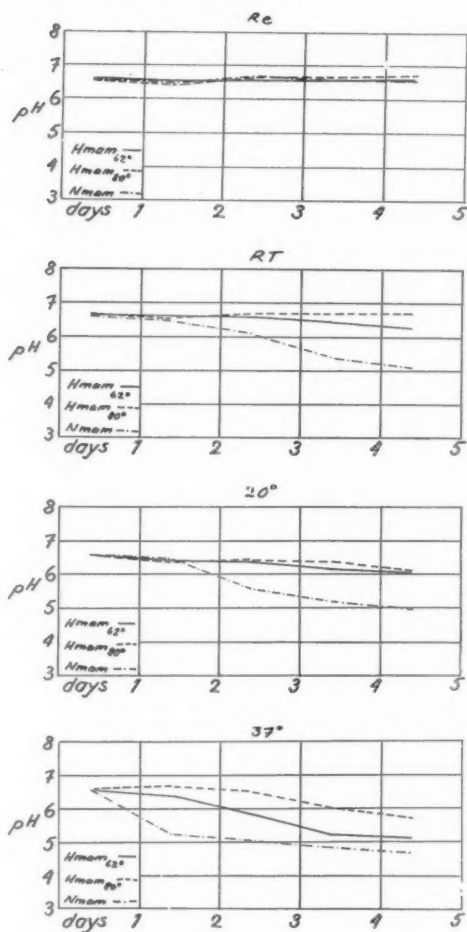


Fig. 1. Preservability of native mare's milk and of mare's milk heated to 62° C and 80° C compared to each other.

Hmam_{62°} = Mare's milk heated to 62° C

Hmam_{80°} = Mare's milk heated to 80° C

Nmam = Native mare's milk

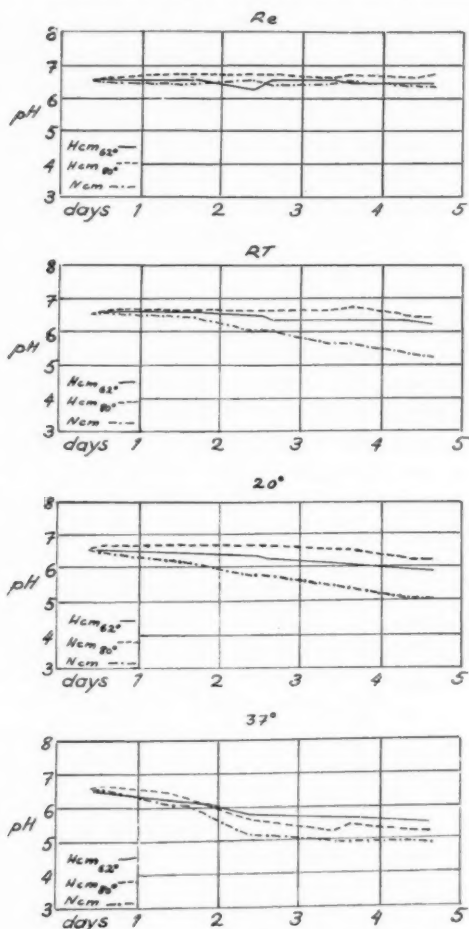


Fig. 2. Preservability of native cow's milk and of cow's milk heated to 62° C and 80° C compared to each other.

but just an indicative of the circumstances and the standard of the stable workers work. In view of this, we have always pasteurized the mare's milk as mentioned before.

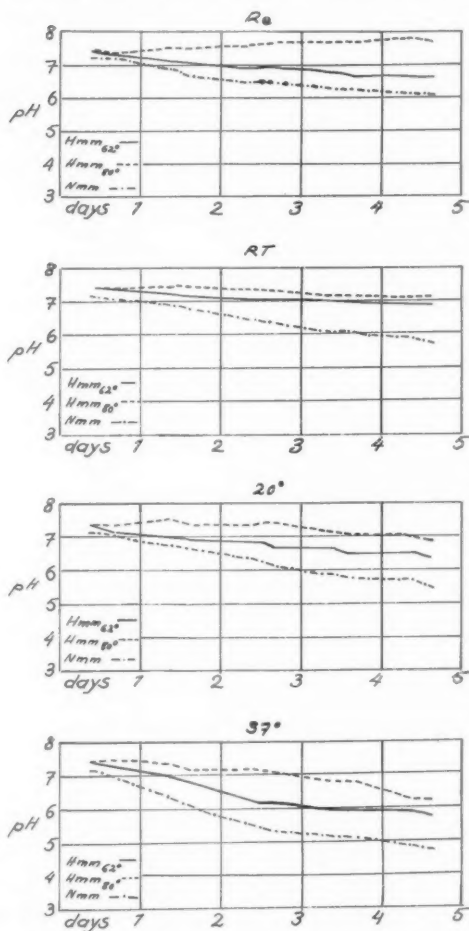


Fig. 3. Preservability of native mother's milk and of mother's milk heated to 62° C and 80° C compared to each other.

The changes in the pH and the taste of milk give some sign of the keeping properties of the milk (SELESTE). In the graphs (Fig. 1, 2, 3) are shown the changes in the pH of untreated milk,

Table

The bactericidity of native mare's milk and of mare's

	0 hours plates											
	Contr.		1:1000		1:10000		1:100,000		1/1 mil.		1/10 mil.	
	T	R	T	R	T	R	T	R	T	R	T	R
Mare No. 6, untreated	250	—	+++	++	+++	++	++	+	+	198	384	181
62°	—	—	++	++	+	+	+	+	+	+	46	46
80°	—	—	++	++	+	+	363	352	124	121	145	145
Mare No. 8, untreated	8	—	+++	+++	++	++	+	+	+	+	44	26
62°	—	—	+++	+++	++	++	+	+	+	+	179	179
80°	—	—	+++	+++	++	++	+	+	77	77	62	61
Mare No. 9, untreated	16	—	+++	+++	+++	++	+++	++	+	+	+	+
62°	32	—	+++	+++	+++	++	+	+	+	+	27	27
80°	1	—	+++	+++	++	++	+	+	281	281	4	4

T = total number of colonies.

R = red colonies (bact. prodigiosus).

of milk kept at 62° C for 20 min., and of milk kept at 80° C for 2 min. Samples of the milks have been kept for five days respectively in a refrigerator, room temperature, 20° C and at 37° C. There is no clear difference between human, cow's and mare's milk. The same holds true for the changes in the taste of different milks.

Lysozymes

A factor which may have some bearing on the keeping properties of milk is the lysozyme, a bactericidal factor found in raw milk. As one of us (SELESTE) has done research on the lysozymes in human and cow's milk, we have wanted to see how mare's milk behaves in this respect.

After the isolation of bacteriolytic ferments by TURRO, FLEMING found a compound which has a great similarity to bacteriophageic lysins. The TURRO ferments are found in all tissues of sheep but not in dogs and only in small quantities in rabbits. They are influenced by temperature in the same way as bacterio-

2.

milk heated to 62° C and 80° C compared to each other.

24 hours plates											
Contr.		1:1000		1:10000		1:100,000		1/1 mil.		1/10 mil.	
T	R	T	R	T	R	T	R	T	R	T	R
+++	—	+++	++	+++	++	+++	++	++	—	++	—
++	—	+++	++	+++	++	++	+	++	+	++	—
++	—	+++	++	+++	++	++	+	++	+	++	—
+++	—	+++	++	+++	++	+++	++	+++	+	+++	+
+	—	+++	++	+++	++	+++	++	++	+	++	+
—	—	+++	+++	+++	+++	+++	++	+++	++	++	+
+	—	+++	+++	+++	+++	+++	++	+++	++	+	+-
+	—	+++	+++	+++	+++	+++	++	+++	++	+++	++
—	—	+++	+++	+++	+++	+++	++	++	++	+	+

phagic lysins. According to TURRO, there are no specific anti-bacterial ferments, but only those that act on the chemical "building-stones" of bacteria or on food substances brought from the exterior. When FLEMING carried out bacteriological studies on rhinitis, he isolated a species of cocci, which was rapidly and intensively dissolved by diluted nasal secretion from the patient. He found a similar lytic agent in most tissues and excretions of the human body, also in animal and plant tissues. Its properties are similar to those of the ferments and FLEMING called it "lysozyme." It acts in solid and liquid culture media bacteriostatically and bactericidally, even in great dilutions. The lysozyme also acts on many others, but not, however, on the coli group. It dissolves living and dead bacteria. It is sensitive to acids and alkalis, and is seriously damaged by heating to 75° C. The optimum temperature for action is between 37° C and 60° C.

In order to investigate the possible lysozyme action in mare's milk we have added to the milk samples of a Bact. prodigiosus suspension in dilutions from 1:1000 to 1:10 000 000. From this a culture on agar plates has been made at 0 and 24 hours to de-

Table

The bactericidity of native cow's milk and of cow's

	0 hours plates											
	Contr.		1 : 1000		1 : 10000		1 : 100,000		1/1 mil.		1/10 mil.	
	T	R	T	R	T	R	T	R	T	R	T	R
Cow's milk No. 9, untreated	6	—	+++	++	565	191	394	183	+++	++	47	13
62°	—	—	++	+	+++	—	340	153	++	+	42	11
80°	—	—	+++	++	+++	++	345	156	127	61	9	4
Cow's milk No. 10, untreated	46	—	+++	++	+++	++	+++	62	++	42	+	12
62°	1	—	++	+	++	+	++	28	130	23	+	—
80°	2	—	+++	++	+++	+	+++	+	++	38	1	—
Cow's milk No. 13, untreated	+	—	+++	++	+++	++	++	+	90	31	64	8
62°	—	—	++	+	++	+	111	23	54	12	6	2
80°	—	—	+++	++	++	+	++	33	65	19	11	4

T = total number of colonies.

R = red colonies (bact. prodigiosus).

Table

The bactericidity of native mother's milk and of mother's

	0 hours plates											
	Contr.		1 : 1000		1 : 10000		1 : 100.000		1/1 mil.		1/10 mil.	
	T	R	T	R	T	R	T	R	T	R	T	R
Human milk No. 1, untreated	296	—	+++	+++	+++	++	+++	++	+++	++	+	16
62°	—	—	+++	+++	++	++	58	55	9	—	4	—
80°	—	—	+++	+++	+++	++	268	240	203	203	2	—
Human milk No. 2, untreated	9	—	+++	+++	+++	+++	374	331	+	+	24	2
62°	—	—	++	++	++	++	363	361	95	95	1	—
80°	61	—	+++	+++	+++	++	++	++	+	259	160	108
Human milk No. 3, untreated	176	—	+++	+++	+++	+++	548	192	+++	++	215	93
62°	—	—	+++	++	541	533	241	236	262	262	—	—
80°	33	—	+++	+++	+++	++	++	+	+	636	++	+

3.

milk heated to 62° C and 80° C compared to each other.

24 hours plates											
Contr.		1 : 1000		1 : 10000		1 : 100.000		1/1 mil.		1/10 mil.	
T	R	T	R	T	R	T	R	T	R	T	R
++	—	+++	++	++	+	+++	++	+++	++	+++	+
—	—	++	+	++	+	++	+	++	+	++	+
—	—	+++	++	+++	+	++	+	++	+	+++	++
+++	—	+++	++	+++	++	+++	++	+++	+	+++	—
++	—	+++	+	+++	+	+++	+	++	—	++	—
+++	—	+++	++	+++	++	+++	++	+++	+	+++	+
++	—	+++	++	+++	++	+++	++	++	+	++	+
71	—	++	+	++	+	++	+	91	6	17	3
+++	—	+++	++	+++	++	++	+	162	32	49	21

4.

milk heated to 62° C and 80° C compared to each other.

24 hours plates											
Contr.		1 : 1000		1 : 10000		1 : 100.000		1/1 mil.		1/10 mil.	
T	R	T	R	T	R	T	R	T	R	T	R
++	—	++	+	++	271	++	208	+	257	+	—
130	—	+++	++	+++	++	++	+	++	+	+	456
—	—	+++	+++	+++	+++	+++	++	+	+	729	729
88	—	+++	+++	+++	++	+	+	+	223	192	112
+	—	+++	++	+++	++	+	+	+	—	—	474
+	—	+++	+++	+++	+++	+	+	+	384	+	+
+	—	+++	++	+++	++	+++	++	++	+	—	78
++	—	++	+	+++	++	+	+	+	330	54	54
28	—	+++	+++	+++	+++	+++	++	+++	++	+	+

monstrate the lysozyme effect. *Bact. prodigiosus* was chosen because of its easily recognizable red colonies. For comparison, we have performed the same tests with human and cow's milk. We have used untreated milk, milk heated to 62° C for 20 minutes and milk heated to 80° C for 2 minutes.

Tables 2, 3 and 4 show that lysozyme effect shows itself more clearly in human (Table 4) and cow's (Table 3) than in mare's (Table 2) milk. It is natural that the effect is weakest in the milk heated to 80° C. In mare's milk, however, the effect is so small that it does not even appear as a decrease of effect in the heated samples.

As a curiosity it may be mentioned that mare's milk is even to-day in use in some parts of Finland as a whooping-cough medicine. In a few plate-cultures we could not demonstrate any inhibition by mare's milk on the growth of *Haemophilus pertussis*.

Digestibility of Mare's Milk in Vitro

Factors Influencing the Digestibility of Milk

It is evident that the factor having most influence on the stomach, as shown in the evacuation time, is the quality and quantity of the casein and as is well known, most of the casein in ordinary cow's milk forms a rather compact and hard curd in the stomach, the digestion of which takes from 3 to 5 hours, whereas the casein of human milk curdles as fine and soft flakes and the evacuation time of the stomach in these cases is from 2 to 2 1/2 hours. In addition, 50—60 % of the protein in human milk consists of albumin and globulin which do not curdle in the stomach. In cow's milk the corresponding fraction is about 15 % of the protein.

In addition, the buffer capacity of cow's milk is considerably greater than that of human milk (GERSTLEY 1933, MARRIOTT and DAVIDSON 1923) and so in consequence, the former needs a much more acid digestive juice in order to reach the same pH. A healthy child can, to a great extent, adapt itself in a few weeks to a change

of food (MARRIOTT and DAVIDSON 1923), but during and after infectious diseases the secretion of both hydrochloric acid and enzymes is considerably lowered for a long period (MARRIOTT and DAVIDSON 1923, DAVIDSOHN 1921) so that in these cases adaptation to an extra strain is not possible.

Attempts have been made to modify cow's milk in order to make it more "physiological". These have been on two lines: to lower the buffer capacity (e.g., by adding hydrochloric lactic, acetic or citric acid) and to cause the casein to curdle in a softer and finer form, either during the preparation (the acid milks) or in the stomach, which can be done by boiling or diluting the milk or by adding "protective colloids" (e.g., oat starch solution) or alkali. BRENNEMAN (1929) is of the opinion that the fineness of the curd is very much more important than that of the buffer capacity, as, for instance, both acid and alkaline milks give equally good clinical results.

In judging the suitability of a milk or milk mixture for infant feeding, the only right criterion is, of course, a large scale feeding experiment with reliable controls. The adaptability of the healthy infant is, however, considerable, and therefore, only the development and state of health of the weakest, least adaptable individuals of each group give some indication of the properties of the foods to be examined. In practice, it is virtually impossible to obtain sufficiently big groups for trials. In consequence, attempts have been made to study the digestibility of different "infant milks" by in-vitro methods, especially in regard to the digestion of the casein curds.

It is natural that an in-vitro system can only roughly imitate the peristaltic movements and continuous secretion of the stomach, not to mention the continuous evacuation of liquid or very finely divided food stuffs; so far as we know, no attempt has been made to imitate the latter. However, the results obtained in such experiments agree fairly well with clinical experience (DOAN and DIZIKES 1942). We have performed digestion experiments with mare's, human, untreated cow's and citric acid milk using a method identical, except for small differences, with that of DOAN and DIZIKES.

Method

The digestion takes place in bags of thin latex rubber, 4 for every sample to be studied; these are suspended in a water bath of 37° C. Into every bag is run a mixture of 0.5 ml of 1-normal HCL, 2 ml of 5 % rennet extract solution (Hausen) and 5 ml of a 0.3 % pepsin solution (U. S. P.), five minutes are allowed for heating of the mixture. Then, using a 50 ml pipette the tip of which had been removed to facilitate the flow, 50 ml of milk heated to 37° C were rapidly blown from the pipette into each bag. A coagulation period of 15 minutes was allowed after which 10 ml of the 0.3 % pepsin solution were added to each bag. At this point, representing the zero time of digestion, the first tube of each sample group was removed for analysis. Immediately after a mechanism was set in motion which rocked the bags to and fro in the water bath at 24 to 30 times a minute. After each half hour of digestion, the pH of the bag's content was lowered by adding 0.75 ml of 1/n normal HCL. The remaining bags of a sample group were removed after 1, 2 and 3 hours of digestion. The bags were emptied into flasks with 25 ml of 40 % formaldehyde and 75 ml of distilled water and the bags were washed and the washings added to the bottles, the contents of which were made up to about 250 ml after which the curd was allowed to harden for at least twenty hours. With the aid of four screens (4, 10, 20 and 40 mesh) and filter paper the curd particles were divided into five fractions according to size. The nitrogen content of these, as well as of the filtrate, was determined by a micro Kjeldahl method (modification of Koch and McMeekin) described by MILLER and MILLER 1948. The results are given as per cent of the total nitrogen of each bag and are shown in fig. 4.

As the amount of HCL for each milk is constant, it is seen that the human milk reaches lower pH levels than the cow's milk with its greater buffer capacity. Mare's milk, the buffer capacity of which is only a little greater than that of human milk, also reaches a low pH. Thus in the mare's milk and human milk samples the pepsin effect is greater, in addition the small size of the casein curds allows a greater surface working area for enzyme action.

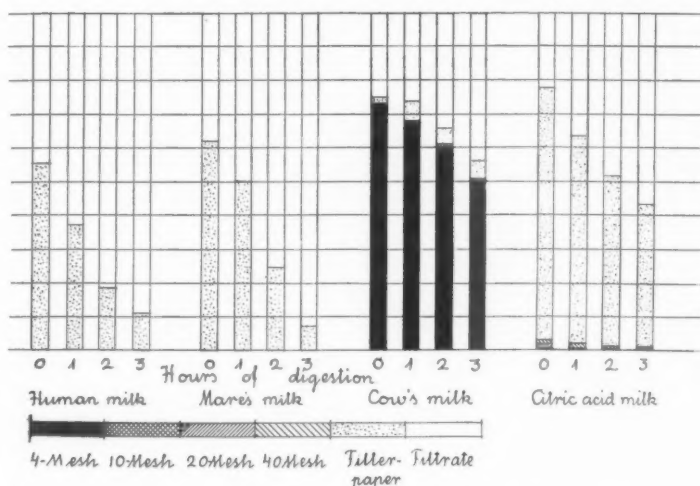


Fig. 4. Digestion of human, mare's and cow's milk in vitro.

As the figure (Fig. 4) shows, the digestibility graphs of mare's milk and human milk are almost similar; this shows that the mare's milk is a very easily digestible milk.

Feeding experiments

The material is shown in table 5. The pH of the faeces and urine is determined with indicator paper (Oxyphen). In calculating the calories, the following values have been used: human milk (HM) 700 calories per liter, cow's milk (CM) 700 cal/l, mare's milk (MM) 410 cal/l, mare's milk with 10 % cream (20 % fat) and 5 % sugar (MM + Cr + S): 745 cal/l, half-milk ($\frac{1}{2}$ M): 570 cal/l, two-thirds milk ($\frac{2}{3}$ M): 770 cal/l, cow's milk with 10 % sugar ($\frac{1}{1}$ M + S): 960 cal/l. The sign "HM + $\frac{1}{1}$ M + S" means that about 10 % of the milk has been " $\frac{1}{1}$ M + S".

In reviewing the table (Table 5), the following facts seem significant.

Weight increase: if we, somewhat arbitrarily, define a weight increase of less than 15 g per day as "poor," 15 to 20 g "fair,"

3/A.R.	I	31.8	2480	1½	HM + ½ M (560-630)	10	152	+26	3.8				
	II	10.8	2710	2	MM (630-650)	16	91	+24	1.3	6	8.5 (8.4-8.5)	8	6.9 (6.5-7.2)
4/E.R.	I	31.8	2660	1½	HM + ½ M (480-510)	10	126	+32	2.1				
	II	8.8	2880	c. 2	MM (570)	9	78	+24	2.3				
5/H.R.	I	31.7	4060	1½	½ M + HM (850)	10	126	+12	1.2				
	II	11.8	4280	2	MM (850)	25	81	+5	1.9	4	7.8 (6.6-8.3)	4	6.1 (5.4-6.5) g+d
	III	6.9	4280	3	HM (900)	5	143	+34	2.0	5	5.2 (4.5-5.7)	5	6.0 (5.7-6.3) g+
6/N.M.	I	14.8	3000	½	HM (600)	10	133	+33	3.2	2	4.5 and 5.7	3	5.8 (5.6-6.1)
(a)	II	24.8	3330	1	MM (600-660)	10	75	+23	3.8	8	8.0 (5.7-8.8)	8	5.9 (5.4-6.9)
7/N.M.	I	14.8	2990	½	HM (600)	10	133	+33	3.3	1	(5.3)	3	6.0 (5.9-6.1)
(b)	II	24.8	3320	1	MM (600-660)	10	75	+23	3.7	7	8.4 (8.1-8.8)	8	6.1 (5.5-6.7) g+d
8/P.K.	I	15.8	4850	2	½ M (1000)	10	116	+15	1.1	3	8.6 (8.5-8.8)	3	5.4 (5.3-5.4)
	II	25.8	5000	2½	¾ M (1000)	10	140	+14	1.8	9	8.5 (8.2-8.7)	9	5.4 (5.2-6.0)
	III	4.9	5070	3	MM (1000)	11	79	+4	1.4	8	8.4 (8.2-8.8)	9	5.5 (5.3-6.0) g+ mixed
	IV	15.9	5080	3	¾ M (1000)	4	150	+55	0.8	1	(8.5)	4	5.8 (5.4-6.1) mixed
9/R.J.	I	20.8	2430	1	HM + ½ m (400-480)	11	112	+36	2.0				
	II	31.8	2820	1½	MM (560-720)	21	85	+25	1.1	14	5.2 (4.5-5.7)	9	6.6 (6.2-7.3) g+
	III	21.9	3340	2	¾ M (720-750)	10	117	+43	1.9	9	8.3 (6.0-8.8)	17	6.4 (5.7-7.6) g+d
	IV	1.10	3780	2½	MM (750)	8	82	-13	0.8	4	7.3 (5.7-8.8)	9	5.6 (5.4-6.6) g+
10/R.A.	I	24.8	6130	9	¾ M × 4 (680-800), veget. × 1	10	—	+3	2.2	8	8.5 (8.1-8.8)	6	6.2 (5.6-6.7) mixed
	II	4.9	6160	9	MM × 4 (800), veget. × 1	16	—	-8	1.4	9	7.8 (5.8-8.5)	9	5.4 (5.1-5.4) mixed
	III	20.9	6030	9½	MM (1000)	6	68	+7	1.2	—	—	12	5.9 (5.4-6.3) mixed
	IV	26.9	6120	9½	¾ M (1000-800)	10	110	+31	1.9	8	7.9 (6.1-8.6)	5	6.0 (6.0-6.1) g- 5.9 (5.4-6.3) g-d

Table 5. Cont.

Patient	Date of beginning of period	Weight at beginning of period	Age, months	Type and quant. (gram/day) of food, Duration of period, days	Cal./kg/day	Development of weight	Number of stools per day	pH				Faecal flora (Gram staining)	
								Faeces		Urine			
								Number of analyses	Mean and border values	Number of analyses	Mean and border values		
10/R.A. V	6.10 6440	10	10	MM (1000)	6	64	+ 7	2.0	5	5	7.1 (6.1-7.8) (8.5)	5.8 (5.4-6.5) 6.1 (6.0-6.3) 6.0	mixed mixed g + d
VI	12.10 6480	10½	10½	MM + Cr + S (1000)	5	106	- 18	1.2	1	3	—	—	—
VII	17.10 6390	10½	10½	½ M (1000)	7	120	+ 0	1.1	—	4	—	—	—
11/V.V. I	26.8 2410	1½	1½	HM + ½ m (440)	10	148	+ 33	2.7	4	4	5.1 (4.8-5.5) (> 8.4)	6.5 (6.0-6.9) 6.5 (6.2-6.9) 6.7 (6.0-7.1) 5.9 (5.4-6.7)	g + d mixed g + d g + d
II	5.9 2700	c. 2	c. 2	MM (480)	6	75	+ 2	0.7	2	6	(8.7)	—	—
III	11.9 2710	c. 2	c. 2	MM (630)	9	92	+ 21	1.2	3	7	—	—	—
IV	20.9 2900	c. 2½	c. 2½	½ M (660)	10	160	+ 35	1.5	6	8	—	—	—
12/H.H. I	16.9 6040	5	5	½ M × 4 (800), veget. × 1	10	—	+ 3	3.2	4	3	8.7 (8.4-8.8)	5.4 (4.8-6.6)	g —
II	26.9 6070	5½	5½	MM × 4 (800), veget. × 1	9	—	—	2.5	6	8	7.7 (6.3-8.8)	5.5 (5.0-6.3)	g —
III	5.10 6060	—	—	MM + Cr + S × 4 (800), veget. × 1	6	—	+ 30	1.5	3	5	(6.9)	5.8 (5.4-6.3)	g —
IV	11.10 6240	6	6	MM + Cr + S (1000)	14	118	+ 11	0.8	3	9	8.5 (8.4-8.6)	5.4 (5.2-5.7)	g +
V	27.10 6420	6½	6½	½ M (800), veget. × 1	9	—	+ 31	1.2	—	—	—	—	—
13/K.M. I	30.9 2600	2½	2½	HM + ½ M (480)	10	124	+ 27	2.4	2	2	(5.4)	(6.8)	g +
II	10.10 2870	—	—	MM + Cr + S (560)	10	105	+ 29	1.5	6	8	5.8 (5.4-6.2)	6.6 (6.0-7.3)	g —

HM = Human Milk.

MM = Mare's Milk.

M = Cow's Milk.

Cr = Cream.

S = Sugar.

d = Dominating.

20 to 35 g "good" (and more than 35 g "excessive") we see that of 19 MM periods the weight increase was good during 7, fair during 4 and poor during 8. Of the poor periods, however, six appear in children (8, 10, 12) who immediately before or after made poor progress on other kinds of milk. The same applies to two periods (10: VI, 12: IV) on "MM + Cr + S."

It is remarkable how a MM diet as poor in calories as 75 to 80 cal/kg per day (4: LL, 6: LL, 7: LL) has been able to give a good increase in weight. This in addition suggests that the digestibility of mare's milk is satisfactory, as 85 to 90 cal/kg per day ought to give a good result; this would mean an amount of 210 to 220 g/kg of body weight daily, which should be within the feeding capacity of an ordinary infant.

Number of Stools

The MM stools are relatively soft, which may make the nurse suspect diarrhea. The table shows, however, that the number of stools during the MM periods does not increase; on the contrary, it seems to decrease in some cases. This would seem to indicate that the MM does not have any irritating effect on the intestines.

pH and Flora of the Stools

Except in patients (2) and (13) the MM stools are clearly alkaline to about the same degree as with the CM mixture. As a contrast, the faecal flora is not so decidedly dominated by the gram negative bacilli, the gram positive bacilli typical to the HM stools are able to maintain their position to some extent, which is probably due to the high milk sugar content of the MM, which continues to ferment in the colon. The organic acids produced are not able to overcome the buffering effect of the phosphates which, as the analyses indicate, is much stronger than on an HM diet. According to FREUDENBERG, the relation Ca : P is 1.87 in HM, 1.37 in CM, 1.97 in MM, i.e., the latter is the greatest. These values of pH of the faeces are somewhat lower than ours (the highest value 8.0).

pH of the Urine

The MM urines are in general less acid than the CM urines, and they are about the same as HM urines. These results agree approximately with those of FREUDENBERG.

Treatment of Acute Intestinal Disturbances

As the fat content is low, mare's milk might be expected to be very suitable for the treatment of infantile diarrhea. It was given systematically to thirty infants of from 1 to 9 months of age as an experiment. Part of them had very severe diarrhea. The clinical course of the disease did not in any way differ from the cases treated with HM during the same period. Vomiting did not occur more frequently than usual. Possibly the consistency of the first stools after the fasting period was a little softer than usual, but the return to normal occurred rapidly. A good increase in weight was not obtained, except in a couple of cases before the feeding was supplemented with whole cow's milk or a liberal amount of sugar.

Summary

1. The properties and suitability of mare's milk from a stud for infant feeding has been investigated.
2. The chemical composition of mare's milk is similar to that of human milk. It is also an albumin milk. The fat content is, however, much lower and the mineral content somewhat higher, this applies especially to the calcium and phosphorus.
3. The keeping properties of the mare's milk received at the hospital, as defined by the reductose test, is poorer than that of first class human and cow's milk. The bacterial flora does not seem to be different from cow's milk. The souring seems to proceed in the same way in all these milks. The lysozyme content seems to be very low.
4. In in-vitro experiments the digestibility of the mare's milk is practically the same as that of human milk, i.e., considerably better than that of cow's milk.
5. In healthy children, even 75 to 85 cal/kg and day was in many cases enough to produce a good increase in weight. If the food consists of mare's milk only, it ought to be given in amounts of 210 to 220 cc per kilogram of body weight. Another way would be to add a quantity of cream and sugar to the mare's milk or give a part of the ration as citric acid milk.

6. The stools during mare's milk feeding are definitely alkaline, approximately similar to cow's milk stools. The character of the faecal flora is between that of cow's milk and human milk stools. The urine is relatively slightly acid.

7. The mare's milk seems to be quite suitable for the early stages of treatment of infantile diarrhea.

H. KALLIALA, ESTER SELESTE et NILO HALLMAN: *L'usage du lait de jument dans l'alimentation de l'enfant.*

1. Les propriétés et l'opportunité du lait de jument pour nourrir les enfants ont été étudiées.

2. La composition chimique du lait de jument est similaire à celle du lait de femme. C'est aussi un lait albumineux. Le taux en graisse est cependant plus bas, le taux des minéraux un peu plus élevé, en particulier pour le calcium et le phosphore.

3. Les propriétés restantes du lait de jument reçu à l'hôpital et définies par le "reductose test" est plus pauvre que celui du lait de première classe de femme et de vache. L'aigreur semble avoir la même origine dans tous ces laits. Le taux de lysozyme semble être très bas.

4. In vitro, la digestibilité du lait de jument est pratiquement la même que celle du lait de femme, c-a-d considérablement meilleure que celle du lait de vache.

5. Chez les enfants sains, il suffit de 75 à 85 calories par kilogramme et par jour dans beaucoup de cas, pour produire une augmentation satisfaisante de poids. Si la nourriture ne consiste qu'en lait de jument on doit donner environ 210 à 220 cm³ par kg du poids du corps. Un autre moyen est d'ajouter une certaine quantité de crème et de sucre au lait de jument ou de donner une partie de la ration en lait acidifié par l'acide citrique.

6. Les selles de l'enfant nourri au lait de jument sont alcalines définitivement, approximativement similaires à celles du lait de vache. Le caractère de la flore fécale est entre celle produite par le lait de vache et celle produite par le lait de femme. Les urines sont légèrement acides.

7. Le lait de jument semble tout à fait convenir pour traiter à son début la diarrhée infantile.

H. KALLIALA, ESTER SELESTE und NILO HALLMAN: *Die Brauchbarkeit von Stutenmilch als Säuglingsnahrung.*

1. Die Eigenschaften und die Brauchbarkeit von Stutenmilch wurde untersucht.

2. Die chemische Beschaffenheit ist ähnlich der Frauenmilch. Sie ist auch eine Albumin-Milch. Der Fettgehalt ist jedoch niedriger und

der Gehalt an Mineralien etwas höher, was sich besonders auf Kalzium und Phosphor bezieht.

3. Die Haltbarkeit der Stutenmilch, bezogen im Krankenhaus, bestimmt durch die Reductaseprobe, ist schlechter als die der erstklassigen Frauen- oder Kuhmilch. Die Bacterienflora scheint nicht verschieden von der der Kuhmilch. Das Sauerwerden vollzieht sich auf die gleiche Weise in allen diesen Milchsor ten. Lysozymgehalt scheint sehr niedrig zu sein.

4. In Vitro ist die Verdaulichkeit der Stutenmilch praktisch dieselbe wie die der Frauenmilch, bedeutend besser als die der Kuhmilch.

5. Bei gesunden Kindern waren 75 bis 85 Kalorien pro Kilogramm und Tag in vielen Fällen ausreichend um eine gute Gewichtszunahme zu erreichen. Wenn die Nahrung ausschliesslich aus Stutenmilch besteht, muss sie in einer Menge von 210 bis 220 cc pro Kilogramm Körpergewicht gegeben werden. Oder es muss eine gewisse Menge Fett und Zucker zur Stutenmilch zugesetzt werden oder man gibt einen Teil der Portion als Zitronensäure-Milch.

6. Der Stuhl während der Stutenmilch-Ernährung ist alkalisch und es ähnelt dem Stuhl bei der Kuhmilch-Ernährung. Der Charakter der Stuhlflora liegt zwischen dem der Stühlen bei Kuhmilch und Frauenmilch. Der Urin ist leicht sauer.

7. Die Stutenmilch scheint sehr geeignet für die Frühbehandlung von kindlichen Diarrhöen zu sein.

H. KALLIALA, ESTER SELESTE y NILO HALLMAN: *Sobre la utilización de leche de yegua para la alimentación de niños.*

1. Se han estudiado las propiedades y conveniencias de la leche de yegua para la alimentación de niños.

2. La composición química de la leche de yegua es semejante a la de la leche humana. Es también una leche albuminoidea. Sin embargo el contenido de grasa es mucho menor y el de minerales algo mayor, especialmente en cuanto al calcio y al fósforo.

3. Las propiedades de conservación de la leche de yegua recibida en el hospital, determinadas por la prueba reductora, son inferiores a las de la leche humana o de vaca, de primera clase. La flora bacteriana no parece ser diferente a la de la leche de vaca. La fermentación parece producirse de igual forma que en todas las leches dichas. El contenido de lisocima parece ser muy bajo.

4. En los experimentos "in-vitro" la digestibilidad de la leche de yegua es practicamente la misma que la de la leche humana, es decir, considerablemente superior a la de vaca.

5. En niños sanos hasta 75 a 85 cal/kg por día era en muchos casos suficiente para producir un buen aumento de peso. Si la alimentación

consiste solamente en leche de yegua debe darse en cantidades de 210 a 220 c. c. por kilogramo de peso. Otro medio sería añadir cierta cantidad de nata y azúcar a la leche de yegua o dar parte de la ración como leche de ácido cítrico.

6. Las deposiciones durante la alimentación con leche de yegua son claramente alcalinas, aproximadamente semejantes a las de la alimentación con leche de vaca. El carácter de la flora fecal está entre el de las deposiciones con leche de vaca y el de las mismas con la leche humana. La orina es relativamente un poco ácida.

7. La leche de yegua parece ser completamente apropiada para los primeros períodos del tratamiento de la diarrea infantil.

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FROM THE BLEGDAM HOSPITAL (EPIDEMIC DISEASES), COPENHAGEN
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Comparative Studies on the Effect in Scarlet Fever of Sodium Penicillin and Procaine Penicillin in Aqueous Suspension

by

TORBEN JERSILD, CHR. HANSTED and JOHN MUNCK

The introduction of procaine penicillin implied a possibility of reducing the number of penicillin injections in the treatment of scarlatinal patients from the two daily injections previously employed [JERSILD (1)] to one injection a day.

Previous studies carried out in the Blegdam Hospital have shown that the treatment of scarlet fever with procaine penicillin (PP) in oily suspension gives satisfactory results when using one injection daily (JERSILD (2), JERSILD and MUNCK (3)). There was a great drawback, however, to this form of therapy, viz., that the penicillin was suspended in oil. So when PP was put on the market in aqueous suspension¹ it was used in the treatment of scarlet fever, and the purpose of these studies has been to see whether the treatment with one daily injection of procaine penicillin in aqueous suspension is just as effective as the treatment previously employed with two daily injections of sodium penicillin (P).

The chemistry of PP has been mentioned in a preceding paper (3). PP is a chemical compound of one molecule procaine and one molecule penicillin. It is almost insoluble in water, and after intramuscular injection the penicillin is liberated slowly. The examination of the penicillin concentration in the blood was carried out on 15 patients after intramuscular injection of 240 000

¹ The PP preparation was kindly placed at our disposal by the Roskilde Medical Company Ltd., Denmark.

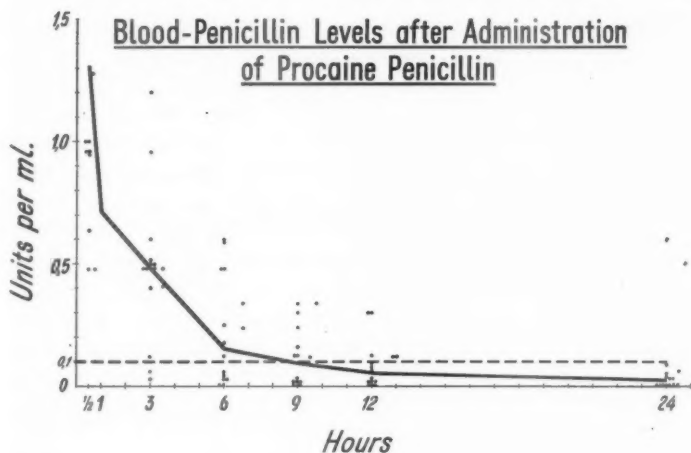


Fig. 1.

—300 000 I.U. of PP in aqueous suspension.¹ The results are presented graphically in Fig. 1.

On comparison of the curve in Fig. 1 with the penicillin concentration in the blood after administration of PP in oily suspension (JERSILD and MUNCK (3)), the concentration after the latter is seen to be considerably higher 3 and 8 hours after the injection—presumably due to the difference in the suspending medium. From Fig. 1 it will be noticed that PP gives a very high penicillin concentration in the blood within 30 min. after the injection and therefore it would be unnecessary to add any ordinary penicillin to the procaine penicillin in order to obtain a rapid initial effect.

As procaine has a toxic effect it has to be considered whether this may possibly influence treatment with PP. In Denmark (Ph. Dan., 1948) the maximal single dose is given as 200 mg (500 mg when given with vasoconstricting drugs). As 300 000 I.U. of PP contains 120 mg procaine, this means that about

¹ The determinations of the penicillin concentration in the blood were performed in the State Serum Institute, Copenhagen, by Dr. Erna Lund, to whom we are greatly obliged for this assistance.

600 000 I.U. of PP contains a single maximal dose of procaine. The slow liberation of procaine reduces its toxicity. But, we think, until more experiences have been obtained, it will be advisable to use sodium penicillin when larger doses are required.

WELCH and HIRSH (4) think that PP is less likely to give untoward effects than procaine and penicillin employed separately. In 2 000 cases treated with PP they found no untoward effect from penicillin.

We have treated 300 patients with PP and noticed no local or general by-effects.

The present material comprises 210 patients with uncomplicated scarlet fever, admitted to the Blegdam Hospital from April to the beginning of July, 1949. The patients admitted on even dates were treated with PP, the patients admitted on odd dates with P, in the following doses:

< 1 year:	60 000 I. U. of P	twice daily for 6 days							
1— 5 years:	90 000	"	"	"	"	"	"	"	"
6—15 "	120 000	"	"	"	"	"	"	"	"
> 15 "	150 000	"	"	"	"	"	"	"	"

In the treatment with PP the same 24-hour dose was given but only as one intramuscular injection a day for 6 days.

The treatment was commenced in the morning after the admission of the patient. Two cultures were made prior to the commencement of the penicillin therapy in order to ascertain the presence of hemolytic streptococci, and additional cultures were made daily during the treatment and 3 times more after discontinuing the treatment. The patient stayed in the hospital for two weeks and returned for reexamination, 4 and 6 weeks after the day of admission, with cultures and microscopy of the urine. In addition, the antistreptolysin titer (AST) and sedimentation rate (SR) were examined on admission of the patients, when treatment was stopped, immediately before discharge, and at the last reexamination.

The two groups of patients treated with PP and P, respectively, were kept separated. On admission, the patients were isolated in small rooms the first two days of treatment.

The present material comprises 101 patients treated with PP, and 109 patients treated with P.

The age distribution (Table 1) was fairly uniform in the two materials.

Table 1.

Age Distribution of the Patients in the Two Groups (expressed as a percentage).

Age in years	1—5	6—10	11—15	16—20	21—25	> 25	Total No. of patients
PP	45.5	34.7	8.0	6.0	1.0	5.0	101
P	52.4	35.8	6.4	0.9	2.8	1.8	109

The temperature of the patients on their admission to the Hospital is shown in Table 2. It shows that the cases in the two groups were of nearly the same severity.

Table 2.

Distribution of the Patients in the Two Groups After the Temperature on Admission (expressed as a percentage).

Temperature on admission	Normal	37.5—38.0°	38.1—39.0°	39.1—40.0°	40.1—41.0°
PP	16.8	22.8	47.5	11.9	1.0
P	12.8	38.6	33.0	12.8	2.8

Cultures for hemolytic streptococci made before the institution of treatment were positive in 56 cases in the P group and 59 cases in the PP group. The group and type distribution of the hemolytic streptococci is recorded in Table 3. It shows a uniform distribution in the two materials.

Table 3.

Group and Type Distribution of the Hemolytic Streptococci Obtained in Cultures prior to the Treatment.

	A1	A4	A6	A9	A17	A22	A28	Ax	More than one type	Total
PP	1	2	4	—	15	4	1	21	11	59
P	2	3	2	1	12	1	—	30	5	56

As criteria of the effectiveness of this treatment we have employed the duration of the primary rise in temperature, the outcome of the cultures, and the number and character of the complication.

The duration of the primary rise in temperature is shown in Table 4 and is seen to be the same for the two groups.

Table 4.

Duration of the Rise in Temperature after the Administration of Penicillin.

	Duration of rise in temperature in days									
	0	1	2	3	4	5	7	8	10	11
No. of patients (%)										
PP	13.9	59.4	11.9	8.9	0	5.0	1	0	0	0
P	13.8	54.1	13.8	9.4	1.8	4.6	0	0.9	0.9	0.9

The outcome of the cultures (Table 5) shows a slight preponderance of positive results in the PP group on the third and fourth days after the commencement of the penicillin therapy and in all the cultures taken when treatment was discontinued. The difference is not significant.

Table 5.

Cultures for Demonstration of Hemolytic Streptococci.

	Before treatment	Days of treatment						After treatment	Re-examination	
		1	2	3	4	5	6		I	II
PP: No. of patients with + hem. str.	59	6	2	3	1	0	0	7	8	9
in %	58.5	5.9	2.0	2.9	1.0	0	0	7.5	8.9	9.5
No. of patients	101	101	101	101	101	101	99	93	90	95
P: No. of patients with + hem. str.	56	7	2	1	0	0	0	4	3	7
in %	51.5	6.4	1.8	0.9	0	0	0	3.9	3.1	7.3
No. of patients	109	109	109	109	109	109	107	103	98	96

The occurrence of complications is shown in Table 6. There is no significant difference between the two groups.

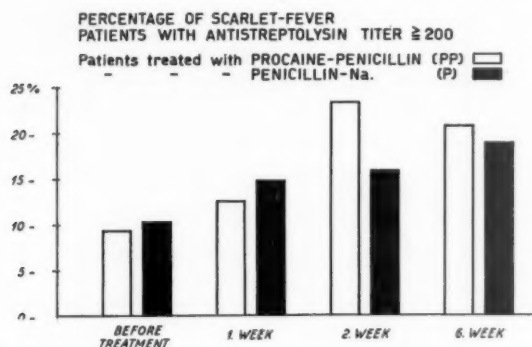


Fig. 2.

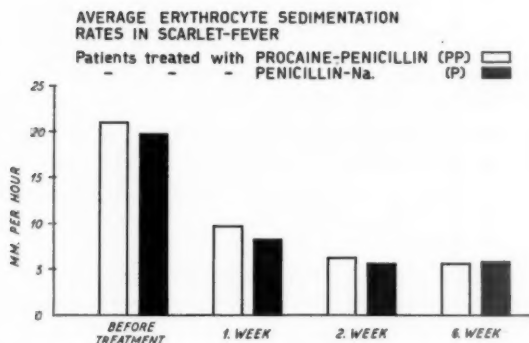


Fig. 3.

Cervical adenitis appeared in only one patient, in the PP group. Cultures showed growth of hemolytic streptococci. The rise in temperature lasted only one day.

Otitis media: 2 patients in the P group had acute suppurative otitis media. One patient had an attack of pneumonia for which he was treated with penicillin. After 4 days he was found also to have otitis media. Cultures were negative. The other patient was readmitted with otitis media 2 weeks after discharge. Before his admission to the scarlatinal ward he had been given pen-

icillin, and cultures from the ear were negative. Cultures from the throat showed growth of hemolytic streptococci.

Mastoiditis did not develop in any instance.

Nephritis was not ascertained in any of the patients.

Only one patient in each group showed the presence of albumin in the urine and that was only at one examination. The patients were not febrile at the time of the albuminuria. Microscopic hematuria was demonstrated on only one occasion in two other patients.

Scarlatinal reinfection occurred in one case in the P group, 10 days after discharge. Another child at home had scarlet fever. Cultures yielded growth of hemolytic streptococci, group A, type X.

The results obtained for AST and SR are presented graphically in Figs. 2 and 3. There is no statistically significant difference in the results obtained from the two groups.

Summary

On comparison of two uniformed scarlet fever groups treated over the same period, with either sodium penicillin (P), two injections daily for 6 days or procaine penicillin (PP) in aqueous suspension, 1 injection daily for 6 days (same daily dose), no definite difference was found in the therapeutic effect as judged from the frequency of complications, duration of the primary rise in temperature, bacteriological examinations, sedimentation rate and antistreptolysin titers.

No local or general untoward effects from the treatment with PP in aqueous suspension were observed.

JERSILD, T., HANSTED, CHR., et MUNCK, J.: *Études comparatives de l'effet dans la scarlatine de la pénicilline-sodium et de la pénicilline-procaïne en solution aqueuse.*

On compare 2 groupes uniformes du scarlatine traités pendant la même période, respectivement avec de la pénicilline-sodium (P), 2 injections par jour pendant 6 jours, et avec de la pénicilline-procaïne (PP) en suspension aqueuse, une injection par jour pendant 6 jours (même dose journalière). On a trouvé aucune différence définitive dans les effets thérapeutiques, en jugeant d'après la fréquence des complications, la durée de la première élévation de la température, les examens bactériologiques, les vitesses de sédimentation et la titre d'antistreptolysines.

Aucuns malencontreux effets, locaux ou généraux, du traitement avec la PP en solution aqueuse ont été observés.

JERSILD, T., HANSTED, CHR., und MUNCK, J.: *Vergleichende Studien über die Wirkung von Natrium-Penicillin und Procain-Penicillin in wässriger Suspension bei Scharlach.*

Beim Vergleich zweier einheitlicher Gruppen von Scharlachkranken, die während der gleichen Zeit jeweils mit Natrium-Penicillin (P) — zweimal täglich eine Injektion während 6 Tagen — beziehungsweise mit Procain-Penicillin (PP) in wässriger Suspension — eine Injektion täglich während 6 Tagen — bei gleicher Tagesdosis behandelt wurden, konnte man bezüglich der Häufigkeit von Komplikationen, der Dauer der primären Temperatursteigerung, der Blutsenkungsgeschwindigkeit und der Antistreptolysintiter keinen wesentlichen Unterschied in der therapeutischen Wirkung feststellen.

Nach Behandlung mit PP wurden weder lokale noch allgemeine nachteilige Folgeerscheinungen beobachtet.

JERSILD, T., HANSTED, CHR., y MUNCK, J.: *Estudios comparativos del efecto sobre la fiebre escarlatina de la penicilina sódica y de la penicilina procaina en suspensión acuosa.*

Se comparan dos grupos uniformes de fiebre escarlatina tratados durante el mismo período, el primero con penicilina sódica (P), dos inyecciones diarias durante seis días, y el segundo con penicilina procaina (PP) en suspensión acuosa, una inyección diaria durante seis días (la misma dosis cotidiana). No se ha demostrado diferencia determinada en el efecto terapéutico a juzgar por la frecuencia de las complicaciones, la duración de la elevación primaria de la temperatura, los exámenes bacteriológicos, la proporción de sedimentación y las concentraciones de antistreptolisina.

No se han observado efectos desfavorables, locales o generales, con el tratamiento de PP en suspensión acuosa.

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Aminopterin Therapy in Leukemia in Childhood¹

by

TORBEN JERSILD and SVEN MEHLSSEN

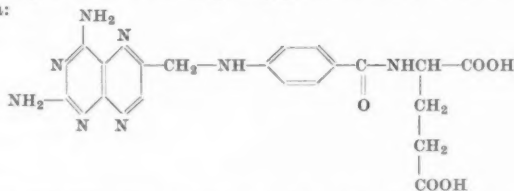
During their studies on leukemias in childhood, FARBER and collaborators (4) found that folic acid and related compounds, such as diopter in and teropter in (pteroyldiglutamic acid and pteroyltriglutamic acid), produced a marked hyperplasia of the bone marrow and of the leukemic infiltrations—"acceleration phenomenon".

They thought, therefore, that an antagonist to folic acid—if such a compound could be produced—possibly might be able to inhibit the progression of the disease or even quite check it.

In collaboration with investigators in the LEDERLE LABORATORIES (6) they succeeded in producing a series of folic acid antagonists, including aminopterin, which proved the most effective of the numerous synthetic folic acid antagonists prepared. But this compound is not only the most effective but also the most toxic in the treatment of the leukemic process.

Chemistry

Aminopterin is 4-amino-pteroylglutamic acid, with the following formula:



It differs from folic acid only by the substitution of an OH radical in the pteridin group with an NH_2 group.

¹ Read before the Danish Pediatric Society on May 31, 1950.

The Theory of its Mode of Action

The mechanism of the activity of this compound may only be guessed at. But, in this connection, BETHELL and SWENDSEID (2) mention an interesting observation. The folic acid content of centrifuged leukocytes was examined. They were obtained from normal persons and from patients with chronic lymphatic leukemia, chronic myeloid leukemia, acute stem cell leukemia and acute myeloblastic leukemia; for each 1 ml centrifuged leukemic leukocytes the folic acid content was found to be respectively 40—180 micrograms (aver. 80), 70—160 (108), 75—220 (146) and 250—800 (460). Furthermore, in 4 cases of chronic leukemia there was a distinct fall in the folic acid content of the leukocytes in response to the X-ray treatment, and this fall was simultaneous with the reduction in the number of immature cells.

As yet it cannot be decided whether the younger and more rapidly growing leukemic cells require larger amounts of folic acid than do the normal cells, or whether the high folic acid concentration is due to defective utilization or some disturbance of the folic acid metabolism. But it may be concluded from these investigations that the folic acid content of the leukocytes of the peripheral blood is directly proportional to the degree of the immaturity of these cells.

WEBER et al. (13) think that the aminopterin effect in leukemia is due to the production of a folic acid deficit, as perhaps the rapidly growing malignant cells are more sensitive to folic acid deficiency than are the normal cells.

FARBER (4) and DAMESHEK (3) have advanced similar theories.

This theory, however, does not appear quite convincing as WEBER et al.—in contrast to FARBER—have not seen any aggravation after 3—4 weeks' treatment with folic acid in three patients suffering from acute leukemia who had developed hematological and clinical remission following aminopterin treatment.

Previous Clinical Experiences

In the latter part of 1947, FARBER and collaborators (4) commenced giving aminopterin to children with acute leukemia. As a result, a number of papers have been published on this form of therapy, especially by American authors.

Most authors have seen remissions more frequently following the treatment of acute leukemia in children, and better results in acute lymphatic leukemia than in other forms. The effect has been least in acute monocytic leukemia.

Remissions were produced in 25—50 % of the cases of acute leukemia (Table 1), while the frequency of spontaneous remission was considerably lower. According to FARBER (5), DIAMOND found spontaneous remission in 10 % of leukemic children prior to the institution of aminopterin therapy, and in the St. Louis Children's Hospital COOKE found spontaneous remissions only in less than 1 % of the cases. In 60 leukemic children we have found complete remission in only 2 patients (about 3 %) (14).

The remissions after treatment with aminopterin last from a few weeks to several months, but complete recovery has never been observed.

In suitable cases aminopterin has a favorable effect upon the bone marrow and peripheral blood; and simultaneously with these changes the general condition of the patient improves. The enlargement of the liver, spleen and lymph nodes diminishes or subsides completely. Under this treatment the bone marrow shows a diminution in the number of leukemic cells or their complete disappearance. The hemoglobin level, the red blood count and the platelet count become approximately normal, and the white blood count falls to within normal or nearly normal limits, no matter whether initially it was abnormally high or low. The number of immature lymphocytes or "blast" forms is reduced more or less completely. Finally, complete aplasia of the bone marrow may appear (FARBER (4)).

WEBER and collaborators (13) found inhibition of the marrow with reduction in both normal and abnormal marrow elements. In contrast to FARBER, however, these authors state that

Table 1.

Folic acid antagonist therapy of acute leukemia.

Authors	Drug employed	Number of patients treated	Percentage of remissions
Farber et al. (5)	Aminopterin Amethopterin Amino-an-fol	60	50
Mills et al. (10)	Aminopterin	21	50
Levin et al. (8)	Aminopterin Amethopterin	10	30
Pierce and Alt (11)	Aminopterin	11	45
Dameshek (3)	Aminopterin Amethopterin Amino-an-fol A-ninopterin	26	34
Meyer (9)	Aminopterin	37	11
Klingberg and Cooke (7)	Aminopterin Amino-an-fol	16	50
Weber et al. (13)	Aminopterin Amethopterin	24	70
Reinhard et al. (12)	Aminopterin Amino-an-fol	17	35

during the treatment the peripheral blood shows both anemia and leukemic cells; megakaryocytes and thrombocytes decrease considerably in number, and a tendency to hemorrhage appears. On account of this they have hitherto employed blood transfusion as a routine adjuvant with the aminopterin therapy. After discontinuance of the treatment, they state, the bone marrow becomes richer in cells, with an increase in the number of normal cells. The most normal picture of the marrow is seen 4—6 weeks after the institution of the treatment. In several of their patients

the number of abnormal cells in the bone marrow fell below 1 % and the peripheral blood picture became normal.

Similar observations have been reported by MILLS and collaborators (10). Under continuous treatment the initial favorable effect diminishes and a gradual increase appears in the number of abnormal cells in the marrow. In rare instances, under protracted aminopterin therapy, aplastic anemia has been observed. Autopsy showed severe hypoplasia of the bone marrow, increasing to aplasia, and often only slight evidence of leukemia or none at all.

Toxic Effects

Most authors state that under this treatment stomatitis and gastro-intestinal ulcerations are frequent, often accompanied by hemorrhage and fever. MILLS et al. (10) found such in more than one-half of the 21 cases treated. But these authors also think that these by-effects are rare, if the total dose of aminopterin is kept under 10 mg. It may be claimed that gastro-intestinal hemorrhages constitute a part of the leukemic picture, but the nature and extent usually exceed the findings in untreated cases of leukemia.

Diarrhea is not rare but it usually disappears rapidly when the treatment is discontinued. Several patients have abdominal pain and a distended abdomen.

Instances of alopecia have been observed.

Several clinicians have tried treating the stomatitis and mucosal ulcerations with liver extract, folic acid or derivatives of folic acid, but without success. The best result is obtained with sulfonamides or penicillin, which indicates that the mucosal ulcerations probably may be due to some secondary infection owing to the leukemia (granulocytopenia), not to any toxic action.

Dosage

The dosage and the duration of treatment vary considerably from one case to another. Generally 0.5—1 mg aminopterin is given intramuscularly daily, until a toxic reaction occurs or there

is a clinical and hematological improvement. Then the treatment is continued with the same dose 2—3 times a week.

Intensive treatment is instituted again at the appearance of signs of a relapse, but now the result is usually not as good as after the first therapeutic course. Sometimes the therapeutic effect is improved when the repeated treatment is instituted with another folic acid antagonist, *e. g.*, A-methopterin or amino-anfol (4-amino-methyl-pteroylglutamic acid and 4-amino-pteroylaspartic acid). Aminopterin has been employed in total doses of up to 89 mg, and some patients have been under this treatment for over one year.

Case Reports

In the Scandinavian literature so far only two reports have been published on aminopterin therapy in leukemia. BERGSTRAND and VAHLQUIST (1) have treated 2 patients suffering from myeloblastic leukemia with blood transfusion and aminopterin, and they saw no remission following the administration of aminopterin. In Denmark, PLUM has presented before the Danish Pediatric Society a single case in which aminopterin produced full remission.

Case 1. Girl, 3 years old. Adm. to this hospital 29/10—24/12/49. Readm.: 17/1—1/3/50.

The child has been well previously. 8 days before admission she became febrile and tired, irritable, and she had lost her appetite. She was hospitalized for observation for endocarditis.

Physical examination: Tired, very poorly and distinctly anemic, but well-nourished. The cervical lymph nodes were enlarged (size of hazel-nut); the spleen was palpable just below the costal margin.

Laboratory tests: Micro-sedimentation rate 47/50 mm. Hb: 50 %. R.B.C.: 2.16 millions. W.B.C.: 10 900. Thrombocytes: 30 000. Differential count: 5 % segment nuclears, 1 % eosinophils, 94 % lymphocytes. Bone marrow, *microscopic diagnosis:* Stem cell leukemia (Fig. 1).

Treatment and course: During the first 2 weeks after admission, the temperature stayed at about 38°. The patient was given penicillin from 7/11 to 14/11. The temperature was normal since.

The treatment with aminopterin is shown in Curve I. After 10 days' treatment with aminopterin the spleen was not palpable, the lymph

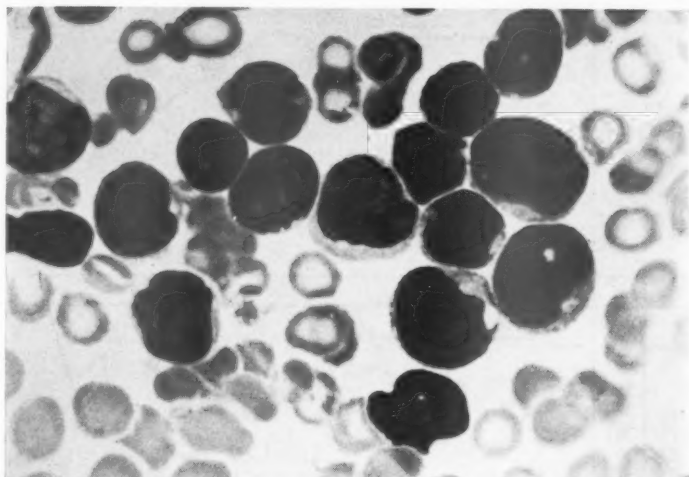


Fig. 1.

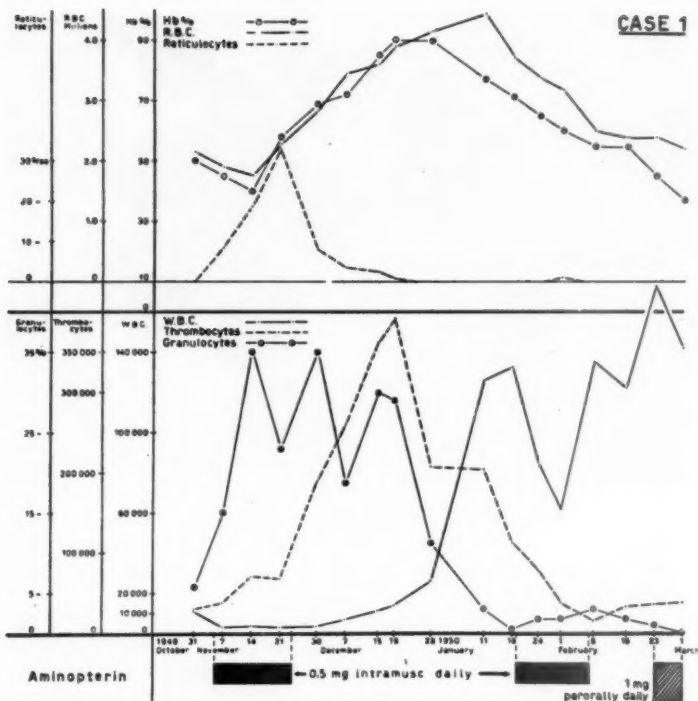
nodes were decreasing in size and the general condition of the patient considerably improved.

Weight on 20/11: 12.100 kg; on 30/11: 13.200 kg; 21/12: 14.430 kg.

At no time was there any sign of hemorrhagic diathesis. After 20 days of treatment (on 20/11) she had voluminous vomiting and diarrhea. 6—8 hours later she suddenly collapsed and was completely unconscious for 2 hours, after which she was exceedingly weak, tired and drowsy. As this attack was considered possibly attributable to aminopterin intoxication, this was discontinued. On the following day she was feeling better and now her general condition improved gradually, so that she was feeling perfectly well at her discharge from the hospital on Dec. 24, 1949.

Readmission on 17/1/50, because the hemoglobin had fallen from 90 to 71 per cent, and the white blood count had kept increasing from 14 900 (19/12) to 26 900 (28/12) and to 126 200 (11/1); the platelet count had fallen from 394 000 (19/12) to 113 000 (17/1).

Physical exam.: General condition fairly good, but the girl gives the impression of being a little more tired than before. The spleen and liver are palpable 3—4 cm below the costal margin. The lymph nodes, which had almost subsided during the first treatment with aminopterin, are now as large as nut kernels in the neck, as beans in the axillae and groins. The temperature is normal.



Curve 1.

Treatment and course: Aminopterin therapy was instituted at once, with a daily dose of 0.5 mg, given intramuscularly, for 20 days (19/1—7/2). During the first 10 days the white blood count falls from 132 000 to 60 000, but even with continued treatment the W.B.C. again rises to 132 000 (Curve I).

During this period of treatment the condition of the patient gradually gets worse, clinically as well as hematologically. This time the enlargement of the spleen, liver and lymph nodes is not influenced by the treatment. The patient was again given aminopterin—this time a double dose (1 mg by mouth from 23/2 to 1/3), but without any favorable effect. Then suddenly the patient had an abrupt rise in temperature and died.

Autopsy (Dr. O. Wanscher): Leukemic infiltrations in the lymph nodes, lungs, spleen, liver, kidneys and bone marrow, which show no

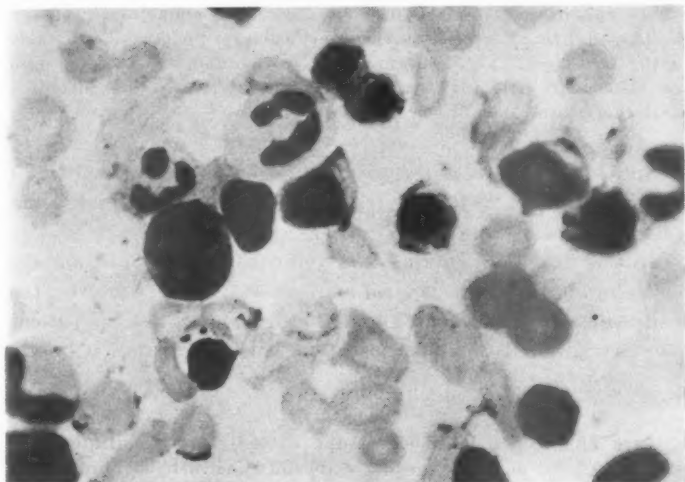


Fig. 2.

other structure besides these leukemic infiltrations, consisting of cells uniform in appearance and presumably belonging to the lymphocytic series.

The result of the *tibial punctures* was as follows: On 31/10: tibial marrow rich in cells—in particular, large amounts of mononuclears of stem cell size (89 %) (Fig. 1). *Microscopic diagnosis*: Stem cell leukemia. (Charles Johansen.) On 17/11: Marrow not particularly rich in cells. 62 % of the cells are of the same type as the dominant cell form in the peripheral blood, i.e., the bone marrow shows a rather marked degree of lymphatic infiltration. The erythropoiesis is well represented (erythroblasts 8 %). No definite diagnosis can be made, but if the diagnosis leukemia has been verified before it seems not improbable that a change in the cytological picture like the present one may have been due to the administration of aminopterin. (H. Gormsen.)—On 3/12: Lymphocytes 39 %, erythroblasts 34 % (a little over the normal 30 %). Some of the lymphocytes look rather immature, and only a few typical blast forms are seen (granulocytes 6 %) (Fig. 2). *Microscopic diagnosis*: Tibial puncture, rich in lymphocytes, with lively erythropoiesis. (H. Gormsen.)—On 21/1: Marrow rich in cells, almost exclusively large typical stem cells (97 %). No erythropoiesis. *Microscopic diagnosis*: Typical stem cell leukemia.—On 11/2: Marrow rich in cells, almost exclusively stem cells (98 %) with an admixture of a few lymphocytes (2 %). *Microscopic diagnosis*: Stem cell leukemia (no change since 21/1).

As mentioned, after the first three weeks of aminopterin therapy the patient had vomiting, diarrhea and collapse, possibly attributable to the treatment. The following series of aminopterin therapy were not associated with any toxic by-effects. Stomatitis and intestinal hemorrhages were not observed.

Subsequently, we had again another opportunity to try aminopterin in the treatment of a patient suffering from acute leukemia.

In this case aminopterin was given entirely by mouth, and the remission obtained was as good as in Case 1. Here, however, the treatment was supplemented by blood transfusion, as the patient had very severe attacks of epistaxis. The case history is briefly as follows.

Case 2. Boy, 12 years old. Adm. to the Finsen Institute, Med. Dep. on 19/2/50. Since the age of 3 years and up until 4 years previously, the patient had been liable to recurrent bronchitis accompanied by fever.

Present illness: 2—3 months before admission the patient became ill with increasing tiredness, uncharacteristic pains in the chest and back, functional dyspnea; in the last month he had also developed subcutaneous hemorrhages. Just before admission the hemoglobin was 55 per cent (3 months before adm. it had been 115 per cent). The patient is said not to have had any fever or itch.

Physical examination: Very thin and pale, but not particularly exhausted. Weight 30.7 kg. Height: 144 cm. The cervical, axillary and inguinal lymph nodes are somewhat enlarged (not kernel size), somewhat indolent and freely movable. The spleen is palpable just below the costal margin. Several fresh and old petechiae are scattered over the body, especially in the legs; also a few larger ecchymoses.

Laboratory tests: Hb: 25 %. R.B.C.: 2.5 millions. W.B.C.: 22 000. *Differential count:* Leukocytes: 2 %. Stem cells: 98 %. *Sedimentation rate:* 49 mm/1 hr. *Sternal puncture I (23/2):* Practically no erythropoiesis or granulopoiesis (0.3 %). Cells almost exclusively of stem cell character (99 %), a little larger than those found in the blood (Fig. 3). *Microscopic diagnosis:* Stem cell leukemia.

Treatment and course: Owing to protracted attacks of epistaxis, the patient was given blood transfusions on 2/3 and 10/3. His condition, clinically as well as hematologically, was getting gradually worse.—On 8/3: Institution of treatment with penicillin (to 28/3) and aminopterin tablets, 1 mg daily. While the temperature had varied between 38°

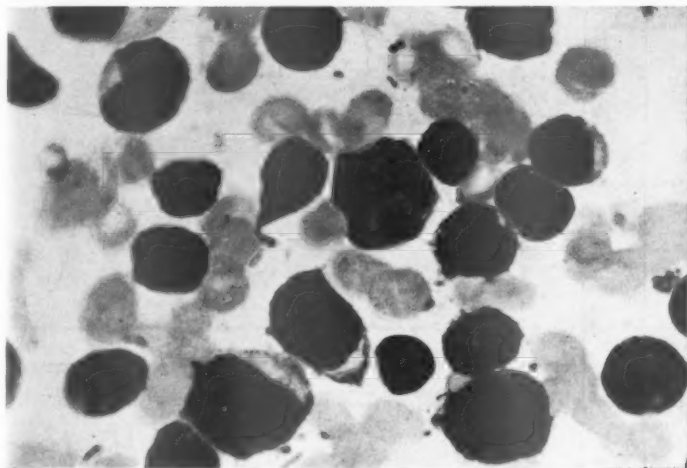


Fig. 3.

and 40° since admission, it now became normal after 12 days of treatment.—10/3: Melena.—18/3: Cervical, axillary and inguinal lymph nodes considerably diminished. Spleen not palpable.—31/3: The attacks of epistaxis have ceased. The general condition of the patient is good.

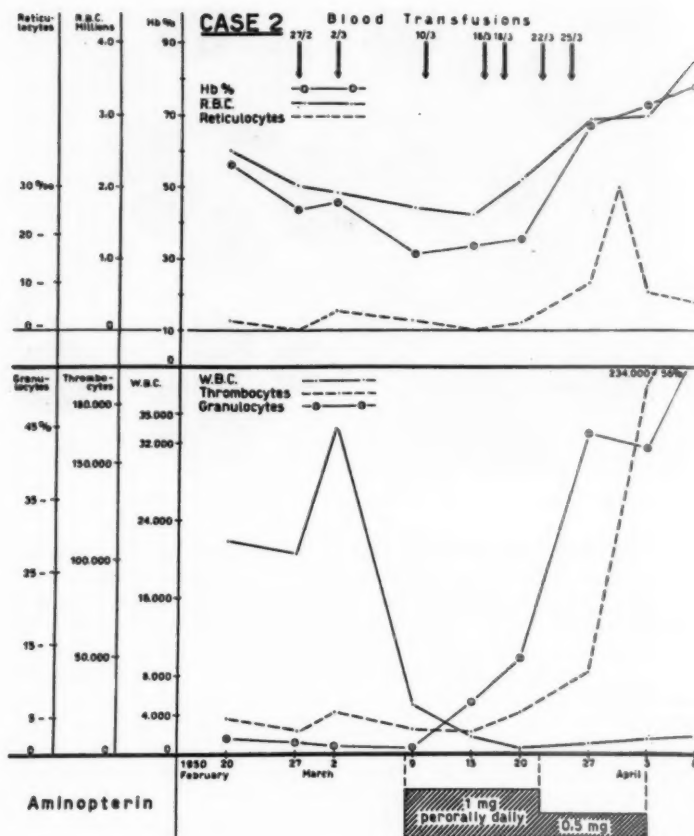
Sternal puncture II (29/3): Lively erythropoiesis (of normal blastic character); granulopoiesis without abnormalities (21 %), lymphocytes (30 %), chiefly small, mature cells, together with a few and slightly more immature cells. The picture is entirely differing from the one seen about 5 weeks before, indicating a satisfactory remission (Fig. 4). *Microscopic diagnosis:* Bone marrow with lively erythropoiesis shifted to the left and a few atypical lymphoid elements (2.7 %).

Weight: 27.6 kg (31/3)—28.2 kg (4/4)—29.0 kg (8/4).

As a result of this clinical and hematological remission, the patient was discharged on 4/4, with aminopterin 0.5 mg by mouth twice a week.

After 3 months of aminopterin treatment the patient feels perfectly well.

Ambulatory reexamination, on May 31: No swelling of peripheral lymph nodes. No enlargement of the spleen. But the *thrombocyte count* has fallen from 280 000 to 40 000 and W.B.C. has increased from 5 000 to 30 000. *Sternal punctate* shows 80 % stem cells (aggravation); as the result of this the dosage of aminopterin is increased to 0.5 mg daily.



Curve 2.

In both of the cases a complete hematological and clinical remission was obtained by treatment with aminopterin—with disappearance of the swelling of the spleen and lymph nodes and return of a normal histological picture of the blood and bone marrow. In contrast to WEBER and collaborators, we found no inhibition of the erythropoiesis during the first period of treat-

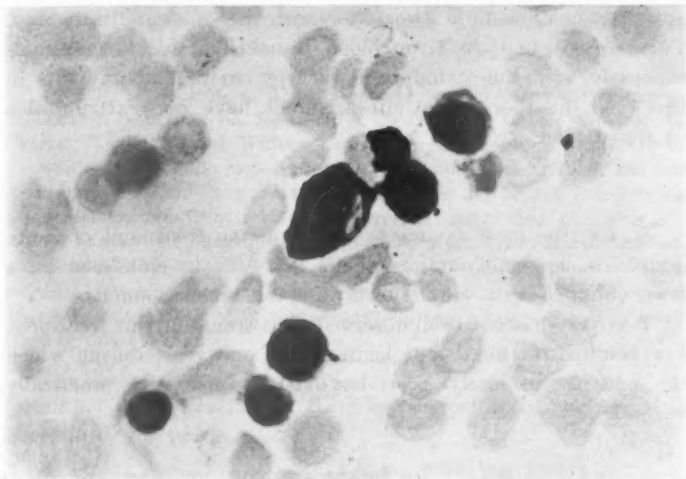


Fig. 4.

ment. Both patients were discharged in apparently good condition with instructions to return for continued ambulatory observation.

After a period of 7 weeks, in which no aminopterin was given, Patient No. 1 had a relapse, and repetition of the treatment proved ineffective.

In Patient No. 2, during the aminopterin treatment the white blood count fell to 500. In spite of this, however, the treatment was continued, and complete remission appeared. The patient has been discharged with a maintenance dose of 0.5 mg aminopterin by mouth twice a week under ambulatory control. Subsequently, however, the blood picture got worse again, and the maintenance dose was therefore increased to 0.5 mg aminopterin daily.

Comments

The course of acute leukemia in childhood is uncertain and, of course, it is conceivable that the remissions in our two cases might have been spontaneous. In both patients, the remission

appeared in immediate association with the aminopterin therapy. Furthermore, in Case 1, no blood transfusion was given simultaneously with the aminopterin therapy, so that at any rate in this case the therapeutic effect cannot have been attributable to transfusion.

Conclusion

So far, the most favorable results in the treatment of acute lymphatic leukemia and stem cell leukemia in childhood have been obtained with aminopterin and related compounds.

Recovery has not been observed, it is true, but this treatment has resulted in remissions lasting over one year, during which the patients in many cases have been apparently practically normal.

Summary

A survey is given of the effect of folic acid antagonists and acute leukemia in childhood. Mention is made of the chemistry, toxicity and action of aminopterin. Two cases of stem cell leukemia treated with aminopterin are reported. In one of them no blood transfusion was given at the same time. Complete remission, clinical as well as hematological, was obtained in both cases. Aminopterin appears to be just as effective when given by mouth as by parenteral administration. One of these patients is still under treatment. It is emphasized that aminopterin may produce complete remission but not recovery.

JERSILD, T., et MEHLSSEN, S.: *Thérapeutique de l'aminoptérine dans la leucémie de l'enfance.*

On rapporte une étude des effets de l'antagonisme de l'acide folique et de la leucémie aiguë dans l'enfance. On fait mention de la chimie, de la toxicité et de l'action de l'aminoptérine. On rapporte 2 cas de leucémie à cellules souche, traités avec l'aminoptérine. Dans l'un d'eux, on ne fit aucune transfusion sanguine en même temps. Une complète rémission, aussi bien clinique qu'hématologique, était obtenue dans les 2 cas. L'aminoptérine semble avoir autant d'effet quand on la prend par la bouche ou qu'on la reçoit par administration parentérale. Un des malades est encore en traitement. Il est souligné que l'aminoptérine peut produire une rémission complète mais pas un rétablissement.

JERSILD, T., und MEHLSSEN, S.: *Über die Aminopterinbehandlung der Leukämie im Kindesalter.*

In einer Übersicht wird die Wirkung von Folsäureantagonisten bei akuter Leukämie im Kindesalter geschildert. Dabei wird auf die Chemie, Toxizität und Wirkungsweise von Aminopterin eingegangen. Es werden zwei Fälle von Stammzellenleukämie beschrieben, die mit Aminopterin behandelt wurden. In dem einen der beiden Fälle wurde keine gleichzeitige Bluttransfusion gegeben. In beiden Fällen wurde sowohl klinisch als hämatologisch ein völliger Rückgang erzielt. Aminopterin scheint bei peroraler oder parenteraler Anwendung gleich wirksam zu sein. Der eine Patient steht noch in Behandlung. Es wird betont, dass man mit Aminopterin wohl einen völligen Rückgang jedoch keine Heilung erreichen kann.

JERSILD, T., y MEHLSSEN, S.: *Terapéutica aminopterina en la leucemia de los niños.*

Se hace un estudio de los efectos antagónicos de ácido fólico en la leucemia aguda durante la infancia. Se menciona la química, toxicidad y la acción de la aminopterina. Se presentan dos casos de leucemia de célula nuclear. En uno no se ha hecho transfusión de sangre al mismo tiempo. Se ha obtenido una remisión completa, tanto clínica como hematológica, en los dos casos. La aminopterina parece ser tan eficaz por vía bucal como inyectada. Uno de los pacientes está todavía en tratamiento. Se remarca que la aminopterina puede producir completa remisión, pero no la curación.

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Die mandibulo-faciale Dysostose, ein neues Syndrom „multipler Abartungen“

von

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I.

Die Lehre von den Embryopathien nimmt im neueren Schrifttum eine besondere Rolle ein. Unter den wechselnden Manifestationsbereichen dieser intrauterinen Entwicklungsstörungen dominieren mesodermale Systemerkrankungen, welche durch den Befall des Stützgewebesystems zu beträchtlichen körperlichen Verunstaltungen führen und Kopf-, Rumpf- und Extremitätenskelett im gleichen Ausmass betreffen können. Gelegentlich beschränken sich congenitale Dysplasien auf den Kiefer-, Gesichts- und Schädelbereich.

Gegenüber dem häufigeren unvollständigen Schluss embryonaler Gesichtsspalten sind Störungen im Entwicklungsablauf des Untergesichtes seltener. Im folgenden wird auf eine Anlagestörung der Unterkiefer-Ohrregion mit deutlicher Beeinflussung des konstruktiven Gesichtsaufbaues eingegangen, welche auf Grund einer überaus charakteristischen Symptomatologie als ein selbständiger Biotypus von anderen Dyskranien abgegrenzt werden kann, dem Bereich der multiplen Abartungen zuzuordnen ist und für die Pädiatrie ein neuartiges Krankheitsbild darstellt. Es handelt sich um einen im frühen Embryonalleben einsetzenden Differenzierungsmangel bestimmter Gewebsareale, die der ersten Kiemenfurche anliegen und in ihrer Gesamtheit erstmalig von FRANCESCHETTI u. ZWAHLEN (1944) unter der Bezeichnung

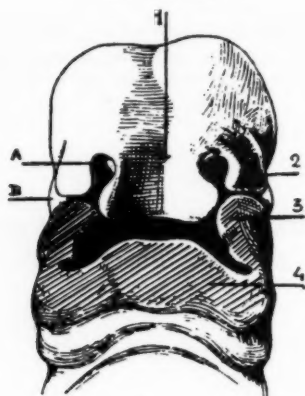


Abb. 1. Schematische Darstellung der primitiven Gesichtsanlagen vor dem Schluss der den Gesichtsschädel bildenden Fortsätze: 1 Stirnfortsatz, 2 lateraler Nasenfortsatz, 3 Jochbeinanlage, 4 Unterkieferanlage. A primitives Nasenloch, B Augenblase. Schraffiert, (3 u. 4) die bei mandibulo-facialer Dysostose betroffenen Differenzierungszentren des Untergesichtes.



Abb. 2. 3 Monate alter Säugling mit Dysostosis mandibulo-facialis: Makrostomie, Mikrotie, Mikrognathie. Antimongoloider Verlauf der Lidachsen mit flügelförmiger Abknickung der Unterlider im äusseren Drittel. Tiefstand des temporalen Augenwinkels, Depression des unteren Orbitalrandes und Einengung der Jochbogenbreite. Pseudoexophthalmus.

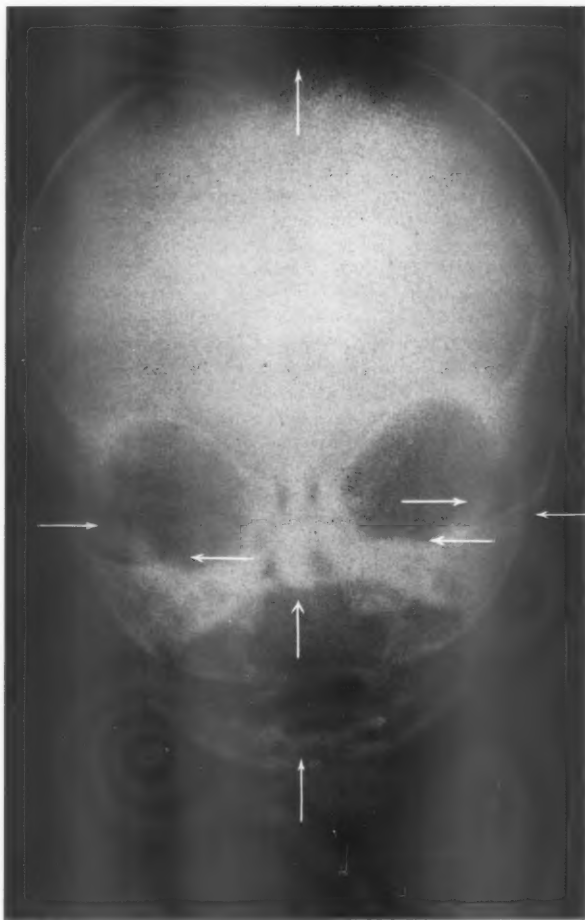
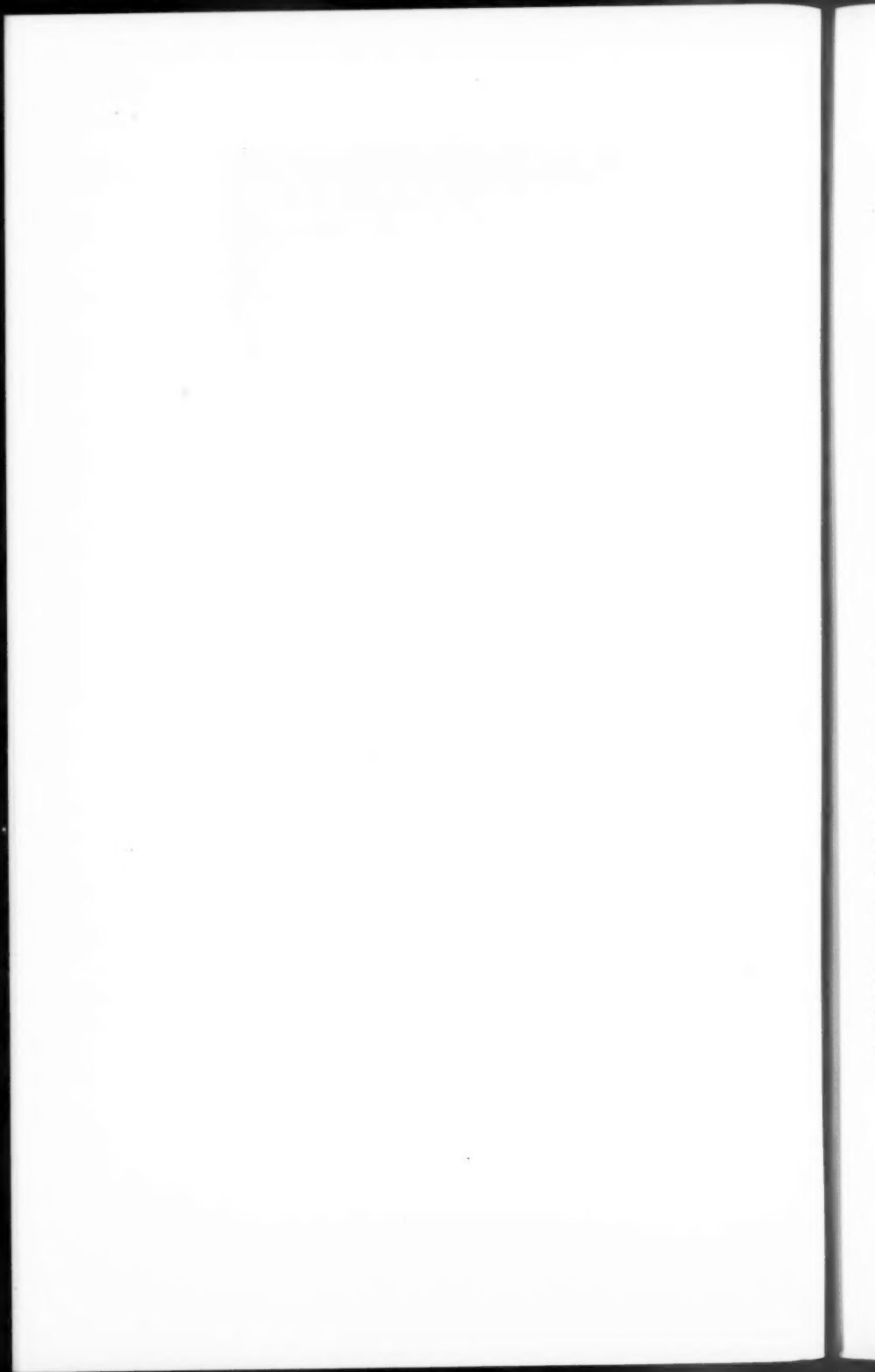


Abb. 3. Sagittalröntgenogramm des Schädels eines 3 Monate alten Säuglings mit Dysost. mand. facialis. Pfeile = Defekte der temporalen Augenhöhlenwände; unregelmässige Kontur der unteren Orbitalränder; Oberkieferspaltbildung; Hemmungsmissbildung der Unterkiefersymphyse; offene Fontanelle; mangelhafter Schluss zwischen Jochbein und Jochbeinfortsatz des Schläfenbeines. Ausgeprägtes Septum nasi.



„Dysostosis mandibulo-facialis“ zusammengefasst wurden. An Hand von 3 eigenen Beobachtungen — wovon 2 in den ersten Lebensmonaten tödlich endeten — soll unter Berücksichtigung der Sektionsergebnisse Klinik und Pathologie dieses Leidens besprochen werden.

Ein besonders aufschlussreiches Beispiel von Dysostosis mandibulo-facialis sahen wir bei einem 3 Monate alten Säugling (J. P. geb. 14.8. 1949), der als 2. lebendes Kind einer jungen Mutter in Steisslage entbunden wurde. Die Schwangerschaft wurde — wie zwei vorausgegangene Fehlgeburten (Mens III u. IV) — mittels Hormontherapie zu halten versucht. In der ersten Hälfte der Schwangerschaft traten geringfügige Blutungen auf; Röntgenbestrahlungen wurden nicht durchgeführt, fieberhafte (exanthematische) Erkrankungen sind nicht bekannt. Ausser diesem missbildeten Kind besitzen die Eltern ein 4-jähriges gesundes Mädchen. In der Familie der Mutter sind auch in der Ascendenz keine Fehlbildungen und Erbkrankheiten bekannt, während die Gesichtszüge des Vaters eine offenbare Ähnlichkeit mit denen des zu schildernden Jungen aufweisen.

Bei der ersten Untersuchung fanden wir ein dystrophisches, aber lebhaftes Kind, das einen kleinen zurückweichenden Unterkiefer besass und an Stelle der Ohrmuscheln zwei wulstige, durch eine Querfurche getrennte Hautfalten aufwies, die an beiden Seiten den Gehörgang vollständig überdeckten. An den weit aufgerissenen Augen fiel eine scharfe Knickung im äusseren Anteil der Unterlider auf, welche mit den tief stehenden hängenden Lidern in den temporalen Augenwinkel übergingen. In diesem Bereich vermisste man die normale Modellierung der Jochbogenhöhe und gelangte bei manueller Palpation in eine grubenförmige Vertiefung, die eine Knochenlücke zwischen Stirn- und Jochbein vermuten liess. Auch der vordere untere Augenhöhlenrand war nicht in gewohnter Weise als eine scharfrandige prominierende Knochensante tastbar, sondern weich besonders in seinem lateralen, vom Jochbein gebildeten Abschnitt, einem unregelmässig begrenzten harter Knochengebilde, welches nicht regelmässig zur Rundung des äusseren unteren Augenhöhlenquadranten anstieg (Abb. 4 u. 5). Durch diese Umgestaltung der knöchernen Augenhöhle verlief die Lidachse in einer dem Mongolismus entgegengesetzten Richtung. Die Mundspalte war auffallend gross, wobei die Mundwinkel wenig ausgeprägt erschienen. Intraoral fand man bei einer bemerkenswerten Oberkieferprognathie eine doppelseitige Spaltung des harten Gaumens mit tief stehendem Vomer. Zunge normal gross, sonst keine Anomalien an den die Mundhöhle bedeckenden Weichteilen.

Bei seitlicher Betrachtung des Schädels fiel neben einer beträcht-

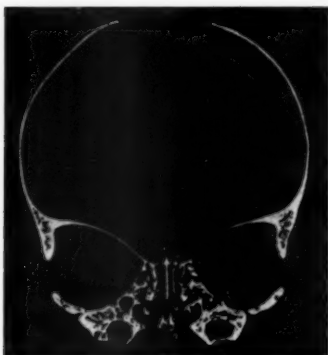


Abb. 4.

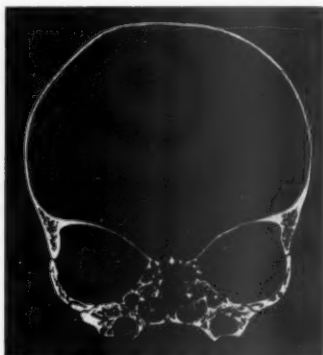


Abb. 5.

Abb. 4. Die in Abb. 3 vorhandenen Anomalien (schematisch) auf einen Frontalschnitt (etwas nach hinten geneigt) durch Augen- und Nasenhöhle eines Neugeborenen projiziert. Durch die Fehlanlage des Jochbeines entsteht ein Defekt in der temporalen Augenhöhle und eine unregelmässige Kontur des vorderen unteren Randes der Orbita. 1 Jochbein, 2 Stirnbein, 3 Lamina cribrosa, 4 untere Muschel, 5 Alveole des 1. Milchmolaren, 6 Sulcus infraorbitalis, 7 Kieferhöhle, 8 Cellulae ethmoideae, 9 tiefstehender Vomer bei doppelseitiger Gaumenspalte.

Abb. 5. Vergleichsbild mit gleicher Schnittführung bei einem normalen Neugeborenen (nach PETER, WETZEL u. HEIDERICH: Hdb. der Anatomie des Kindesalters). Man beachte den Kontakt der Joch- und Stirnbeinhöcker in der Sutura zygomatico-frontalis und die gleichmässige Rundung der unteren Orbitahälfte.

lichen Mikrognathie des Unterkiefers retroaurikulär eine muldenförmige Einsenkung auf. Die vordere und hintere Schädelgrube fanden sich in deutlicher Ausprägung. Der Kopfumfang betrug 35 cm bei weit offener grosser Fontanelle. Die Schädelnähte waren ohne Auftreibungen und Deformierungen.

Eine d. a. Schädelaufnahme verdeutlicht den Defekt der knöchernen Augenhöhlenwandung, wobei zu erkennen ist, dass eine Fehlanlage der Jochbeine besteht, derart, dass der Stirnbeinfortsatz des os zygomaticum so verkümmert ist, dass er den Jochbeinfortsatz des Stirnbeines nicht erreicht, während dieser Abschnitt sich bei normal entwickelten Kindern als eine gleichmässige geschlossene Rundung darstellt. An der Unterkiefersymphyse findet sich ein hypoplastischer Bildungsfehler (Abb. 3). In der transversalen Schädelaufnahme kommt die Hypoplasie der Unterkieferspange, vor allem der aufsteigenden Äste, mit dem wangenwärts verlagerten, obliterierten Gehörgang deutlich zum Ausdruck. Die Schädeldecke zeigt eine normale Knochenzeichnung ohne Auflage-

rungen und Verdichtungen. Sella nicht vergrößert. Die Schlüsselbeine sind bds. angelegt; am unteren Ende des Brustbeines findet sich eine trichterförmige Einziehung. Das übrige Rumpf- und Extremitätenskelett ist auch röntgenologisch frei von Deformierungen.

Nach fachärztlichem Untersuchungsbefund sind Augen und Augenhintergrund frei von pathologischen Veränderungen. Blutsenkung, Differentialblutbild und Urinwerte liegen im Bereich physiologischer Schwankungsbreiten. Bemerkenswert erscheint eine basophile Tüpfelung der Erythrocyten und das Auftreten basophiler Granulocyten im Blutausschlag.

Nach den in vergangenen Jahrzehnten unter verschiedenen Namen mitgeteilten Beobachtungen dieser Abartung lässt sich trotz der Vielfalt auftauchender Variationsmöglichkeiten ein Standardtyp mit folgenden obligaten Zeichen umreißen:

1. Breite Mundspalte (Makrostomie) mit Tendenz zu schrägen Gesichtsspalten, unvollständigem fehlerhaften Schluss derselben und persistierenden (blinden) Fistelgängen.

2. Kümmerwuchs der Ohren (Mikrotie) und des Unterkiefers (Mikrognathie).

3. „Antimongoloider“ Verlauf der Lidachsen mit Tiefstand der äusseren Augenwinkel und flügelförmiger Abknickung der Unterlider.

4. Hypo- und Aplasie der Jochbeine mit konsekutiver Beeinflussung des Oberkiefermassivs (Gaumenspalten) und der unteren Orbitalabschnitte.

Mit den genannten Symptomen treten eine Reihe degenerativer Stigmata auf, von denen an dieser Stelle Wirbelsäulen-, Thorax- und Extremitätenmissbildungen genannt seien. Als Folge der frühzeitigen Fruchtschädigung werden ferner Schwerhörigkeit, geistige Debilität und in späteren Jahren auf der Basis unterentwickelter Kiefer entstehende Dentitions- und Okklusionsstörungen, am Schädeldach Impressiones digitatae beobachtet.

Als Leitsymptom der Dysostosis mandibulo-facialis ist ein auch bei Abortivformen und sonstigen nicht manifest erkrankten Sippenmitgliedern häufiger, von nasal nach temporal abfallender Verlauf der Lidachsen anzusehen. Die Entstehung dieser Eigentümlichkeit ist auf das Fehlen einer knöchernen Basis am äus-

seren Augenwinkel zurückzuführen, wodurch der temporale Lidwinkel nicht fixiert werden kann und schlaff herunterhängt. Während bei normal entwickelten Kindern diese Augenhöhlenabschnitte durch Fortsätze des Stirn- und Jochbeines gebildet werden (s. Abb. 5), welche schon zur Zeit der Geburt in der Sutura zygomatico-frontalis zusammentreffen, klappt bei der Dysostosis mandibulo-facialis zwischen den genannten (rudimentären) Fortsätzen ein Spalt (Abb. 3), sodass die darüberliegenden Weichteilbedeckungen eine formgebende Unterlage entbehren. Anschaulich vermögen die Verhältnisse beim Mongolismus mit den in umgekehrter Richtung verlaufenden Lidspalten die Bedeutung einer knöchernen Basis für die Entstehung dieser Anomalie zu unterstreichen. Hier findet sich ein normaler Schluss der seitlichen Augenhöhlenabschnitte, aber Hypoplasien der an der Bildung der nasalen Orbita beteiligten Regionen des Nasen-Oberkiefergerüsts mit Einschluss des Zwischenkiefers, wobei rudimentäre oder auch fehlende Ossa nasalia (VON DER SCHEER, KREITZ, KREYENBERG u. a.) beobachtet werden.

In Verbindung mit diesen dysosteogenetischen Störungen sind bei der Dysostosis mandibulo-facialis die selten vermissten flügel-förmigen Knicke der Unterlider entstanden zu denken, welche bis zu Lidkolobomen, Anomalien des Wimpernbettes, der Meibomschen Drüsen und des Tarsus führen. Infolge dieser Lidveränderungen, welche auch das Oberlid betreffen können, wird der sonst normal entwickelte Augapfel oft weit entblösst, sodass der Eindruck eines Exophthalmus entsteht, welcher mit den genannten Bildungsfehlern des Gesichtsschädels, insonderheit der eingeschränkten Jochbogenbreite, des gradlinigen Überganges von Nasenrücken und Stirn mit der Oberkieferprognathie, der breiten Mundspalte, dem fehlenden Kinnmassiv sowie den Aurikularresten einer „fish-like physiognomy“ nahe kommt (s. Abb. 2).

Ausser den Missbildungstendenzen des Gesichtsschädels werden — wenn auch in einem weit geringeren Umfang — Fehlbildungen am Rumpf und an den Extremitäten sowie am (mesodermalen) Stützgerüst innerer Organe beobachtet. Wir sind auf diese für die nosologische Stellung des Syndroms wichtigen Zusammenhänge an anderer Stelle ausführlicher eingegangen (WEY-

ERS, 1950) und erwähnen hier zur Vervollständigung des Krankheitsbildes die auch pathologisch-anatomisch erwiesenen angeborenen Lungendystopien in Form von Atelektasen, Lungenblähung u. dergl. Von Wichtigkeit sind auch Wirbelsäulenanomalien, wie sie bei mandibulo-facialer Dysostose häufiger zur Ausbildung gelangen und mit Occipitalisation des Atlas, cuneiformen Wirbelfragmenten und Skoliosen der Hals- und Brustwirbelsäule einhergehen. Es erscheint uns von Bedeutung, nachdrücklich darauf hinzuweisen, dass eine Generalisationsneigung der Fehldifferenzierung im mesodermalen Gewebsbereich, analog dem Verhalten anderer degenerativer Dysostosen: Progerie, Arachnodaktylie, Dysostosis cleido-cranialis u.a. auch bei dem mandibulo-facialen Syndrom unverkennbar ist, ein Sachverhalt, der uns veranlasst hat, statt der bisherigen nur Kiefer-Gesichtsveränderungen berücksichtigenden Terminologie die umfassendere Bezeichnung „Dystrophia mesodermalis congenita Typ FRANCESCHETTI“ vorzuschlagen und diese dem Typ GILFORD, MARFAN, MARIE-SCHAUTAUER an die Seite zu stellen.

Besondere Ausmasse können die genannten Anomalien bei einseitiger Manifestation des mandibulo-facialen Prozesses erreichen (FRANCESCHETTI u. KLEIN, BREGEAT u. NAUD, eigene Beobachtung). Der Charakter dieser Entwicklungsstörung wird dabei besonders deutlich, weil neben der Vergleichsmöglichkeit mit der gesunden Seite einige bemerkenswerte Befunde erhoben werden können. Ohne auf Einzelheiten solcher Verlaufsformen näher einzugehen, erscheint mir der Hinweis von Bedeutung, dass hierbei übereinstimmend Entwicklungsstörungen der Wirbelsäule auftreten die einen Zusammenhang mit dem KLIPPEL-FEIL'schen Syndrom nahe legen. Die Besonderheiten unilateraler Dysostosis mandibulo-facialis — auf die noch zurückzukommen sein wird, und worüber in ausführlicher Weise FRANCESCHETTI, BROCHER u. KLEIN berichten — konnten wir durch einen angeborenen Hydrocephalus und die den betroffenen Wirbelsegmenten zuzuordnenden Lungenveränderungen bereichern. Auf der befallenen Seite fanden sich ferner die knorpeligen Anteile und häutigen Anlagen des Ohres völlig rudimentär entwickelt, während die Tuba Eustachii sowie das Ostium pharyngicum nicht angelegt waren.

Mit diesen atypischen Fällen treten neuro-muskuläre Ausfallserscheinungen im Versorgungsgebiet des Nervus facialis auf, welche gemeinsam mit Muskelagenesien des M. frontalis, des M. stylohyoideus und des hinteren Biventerbauches beschrieben wurden. Eine Läsion des die Gesichtstrophik beherrschenden N. facialis wird durch den Verlauf im retroaurikulären Knochenmassiv, welches bei dieser Anlagestörung regelmässig betroffen zu sein pflegt, verständlich.

II.

Die Eigenart der aufgezeichneten Befunde lässt es berechtigt erscheinen, auf die entwicklungsgeschichtlichen Grundlagen dieser Dysosteogenese einzugehen. Zum Verständnis wird es nötig sein, auf die Verhältnisse bei Keimlingen im Alter von 6 bis 8 Wochen — der vermuteten Manifestationsperiode mandibulo-facialer Disproportionalität — hinzuweisen. Während dieser Entwicklungsphase differenzieren sich aus den durch die Schlundfurchung getrennten dorsalen Segmenten des Mandibular- und Hyoidbogens die Anlagen des äusseren und inneren Ohres. Eine Störung dieser als unregelmässige Höcker in Erscheinung tretenden primitiven Ohranlagen zieht das Auftreten der späteren Aurikularreste, wie sie bei der Dysostosis mandibulo-facialis gesehen werden, nach sich (Abb. 2). Da aus der Zwischenstrecke der betroffenen Mandibularanteile der Unterkiefer gebildet wird, ist dessen Kümmerwuchs, vor allem der aufsteigenden Äste und auch ein Bildungsfehler im Symphysenabschnitt erklärlich. Zu den Aufbauelementen des 1. Kiemenbogens zählt ferner die Jochbeinanlage, deren Fehlentwicklung die Einengung der Jochbogenbreite und die Defekte der äusseren Augenhöhlenwandung bedingen, wie es die schematische Zeichnung der primitiven Gesichtsanlagen (Abb. 1) zu erkennen gibt. Eine generalisierte Entwicklungsschwäche dieser mesodermalen Bildungszentren legt die Vermutung nahe, dass auch der normale Schliessungsmechanismus der den Gesichtsschädel bildenden Fortsätze behindert wird, als dessen Folgeerscheinung die in überzufälliger Häufigkeit bei mandibulo-facialer Dysostose vorhandenen Gaumenspalten (BERRY, McENERY u. BRENNEMANN, KILNER, FRANCESCHETTI

u. KLEIN (FALL 3 u. 4), unsere Beobachtungen 1—3) angesehen werden können. Dabei bedarf der Erwähnung, dass in den bis heute (einschliesslich der Weltliteratur) mitgeteilten Berichten nicht einmal eine Hasenscharte beobachtet wurde.

Die genauen Lage- und Grössenbeziehungen der Kiefer-Ohr-Jochbeinregion mag eine Profilaufnahme eines 4 Monate alten Patienten mit mandibulo-facialer Dysostose (Abb. 7) wiedergeben. Im Vergleich dazu seien die normalen Verhältnisse bei einem Keimling mit einer Scheitel-Steissbeinlänge von 21,35 mm (Abb. 6) angeführt, um den Entwicklungsrückstand des Untergesichtes gegenüber einer ungestörten Weiterentwicklung des Schädels zu demonstrieren. Ausser diesen grundsätzlichen Abweichungen gehört eine genaue Kenntnis der den Symptomenkomplex von FRANCESCHETTI charakterisierenden Eigenarten dazu, um auch Mikroformen, atypische und unvollständige Verlaufsformen dieser Abartung einordnen zu können. Nachdem so der Diagnose keine wesentlichen Schwierigkeiten mehr im Wege stehen, gewinnen Ätiologie und Pathogenese des Leidens eine besondere Bedeutung.

Das eigenartige Krankheitsbild erinnert zunächst an das im Laufe der vergangenen Jahre in zunehmendem Masse beschriebene Syndrom der Rubeolenembryopathie (GREGG, EVANS, SWAN, MANN, HENKEL u.a.) und hat zudem Gemeinsamkeiten mit der infantilen Toxoplasmose (SABIN, COLLAHAM, RUSSEL u. SMITH, COVENETZ) aufzuweisen. Für beide Erkrankungen gilt die Vorstellung, dass im frühen Embryonalleben Toxine auf diaplazentarem Wege den Foeten schädigen. Wir wissen aus den grundlegenden Studien SPEMANNs, dass die Natur dieser Noxen, welche die Plazentarschranke durchbrechen, verschiedenartig sein kann. Nach heute gültiger Auffassung finden sich Auswirkungen vorwiegend in den Organsystemen, welche sich zum Zeitpunkt der einwirkenden Schädlichkeiten im Stadium der grössten Entwicklung (Teilung) befinden, wobei eine Keimblattelektivität nicht gewahrt sein braucht. In entsprechend frühen Entwicklungsstadien sind die Keimblätter noch in inniger Verbindung miteinander, sodass eine universelle (infektiöse) Schädigung Abkömmlinge des Ento-, Meso- und Ektoderms beeinflussen kann. In anschaulicher Weise lassen sich diese Vorstellungen an den

mitgeteilten Beobachtungen von Rubeolen- und Toxoplasmoseinfektionen demonstrieren. Die Sichtung eines umfassenden Beobachtungsgutes dieser Embryopathien hat gezeigt, dass die kritischen Perioden der Entstehung bestimmter Organschäden (Herz, Auge, Ohr, usw.) zeitlich zu begrenzen sind. Hiernach kann als erwiesen angesehen werden, dass vor der 6. Embryonalwoche Augen und Herz zu Störungen des normalen Entwicklungsablaufes disponiert sind, während die Ohranlagen noch nach diesem Zeitpunkt dem destruirenden Einfluss exogener Schäden unterliegen.

Dieser Hinweis ist für die mandibulo-faciale Dysostose nicht bedeutungslos, da primär Ohranlagen und angrenzende Gesichtsabschnitte betroffen sind, Zentren, die nach übereinstimmenden entwicklungsgeschichtlichen Untersuchungen (HISS, HAMMAR, STREETER, v. HOCHSTETTER) etwa um die 7. Embryonalwoche differenziert werden. Mithin wird verständlich, dass in den bis heute vorliegenden Krankenberichten über die „Dysostose mandibulo-faciale“ nie ein Herzfehler und keine pathologischen Veränderungen am Auge gefunden werden, während dies bei den genannten Embryopathien regelmässig der Fall ist. Mit diesen Bildungsfehlern können selbstverständlich auch Fehlentwicklungen der Ohren auftreten, deren Ursache in der frühzeitigen und anhaltenden Wirkung infektiöser Noxen zu suchen ist.

Die Art der einwirkenden Schädigungen spielt sicherlich eine untergeordnete Rolle, wobei betont werden muss, dass nach neueren Erhebungen ausser Rubeolen und Toxoplasmose auch Masern und Mumps, Herpes Zoster und Scharlach (SWAN, TOSTEVON u. BLACK), Varizellen (LAFORET u. LYNCH), Influenza, Hepatitis, Poliomyelitis (DOGRAMACI u. GREENE) pathognomonisch bedeutsam werden können. Wir sind ferner durch den Befund eines enormen Hydrocephalus mit hohen Eiweisswerten und geringer Zellzahl im Liquor (s. hierzu die Mitteilung von GASSER u. SCHWARZ), ein für die D. m. f. ungewöhnliches Ereignis, auf eine mögliche infektiöse Ätiologie hingewiesen worden (WEYERS [3]). Obgleich neben der cyto-albuminären Dissoziation des Liquors und dem entzündlichen Hydrocephalus kein bindender Anhaltspunkt für einen gültigen Vergleich mit Toxoplasmose vorhanden ist, möchten wir



Abb. 6.



Abb 7.

Abb. 6. Menschlicher Keimling mit einer Scheitel-Steißbeinlänge von 21,35 mm¹, der die topographischen Lage- und Größenbeziehungen der Ohr-Unterkiefer-Jochbeinregion während der embryofetalen Entwicklung veranschaulicht. Man beachte die beträchtliche Mikrognathie des Unterkiefers und die Einsenkungen im temporalen Augenabschnitt sowie im retroaurikulären Knochenmassiv.

Abb. 7. Die Persistenz der in Abb. 6 genannten embryonalen Gesichtsbeziehungen zeigt die Entwicklungshemmung bei einem 3 Monate alten Jungen mit Dysostosis mandibulo-facialis: Mikrognathie, Kümmerwuchs des Ohres, Einsenkungen der Jochbein- und Retroaurikularregion.

doch die Frage offen lassen, ob nicht eine um die 7. Embryonalwoche einsetzende exogene Noxe die für mandibulo-faciale Dysostose typischen Veränderungen bewirken kann. (Der Frage der Rhesusinkompatibilität, welche für die mit Lungenatelektasen, Emphysem und Lungenblähung vergesellschafteten cystischen Pancreasfibrose (Dysporia entero-broncho-pancreatica congenita familiaris) von GLANZMANN u. WEGELIN angeschuldigt wird, wurde nicht weiter nachgegangen.)

Auf der anderen Seite erweckt die Beständigkeit der beim mandibulo-facialen Syndrom gefundenen Veränderungen mit

¹ Für die Vermittlung dieses von Prof. v. HOCHSTETTER (Wien) entliehenen Originals bin ich Herrn Prof. H. MATHIS (Graz) zu Dank verpflichtet.

fixierter Lokalisation im Unterkiefer-Ohrbereich den Eindruck einer ausgesprochenen Organdisposition. Mit HURST, MANN u. ALBAUGH sind wir geneigt, hierfür trophische Störungen mitverantwortlich zu machen.

Unter trophischen Störungen werden solche des Gefäß-Nervensystems verstanden, denen die Umgestaltung des Gewebes in Form von Wachstums- und Rückbildungsvorgängen unterliegt. Es ist als sehr wahrscheinlich zu betrachten, dass es ein eigentlich „trophisches Nervensystem“ nicht gibt, sodass man auf die trophischen Komponenten des bekannten und nachweisbaren vegetativen Nervensystems zurückgreifen muss, wobei heute allerdings noch die Frage offen bleiben muss, ob diesem „parenchym-innervierenden“ Teil des vegetativen Nervensystems eine strukturverändernde Wirkung zukommt (DÖRING).

Festzuhalten ist aber, dass sowohl Beziehungen zwischen sensiblen und motorischen Nerven als auch koinnervatorische Verbindungen der ersteren mit dem vegetativen Nervensystem nachzuweisen sind. Diese trophischen Anteile motorischer und sensibler Nerven und ihre Verbindungsbahnen zum vegetativen Nervensystem sind es, denen bei der Entstehung symmetrischer Bildungsfehler eine massgebliche Bedeutung einzuräumen ist.

Wir haben an anderer Stelle auf die Bedeutung weiterer exogener Einflüsse für die Entstehung intrauterin erworbener Missbildungen — insonderheit auf Unstimmigkeiten des hormonalen Milieus des mütterlichen Organismus — hingewiesen und hierbei die Vermutung ausgesprochen, dass auch mechanische Schädigungen (Fruchtabtreibung u. dergl.) bedeutsam werden können. In einem Falle mit Halbseitenlokalisation mandibulo-facialer Dysostose haben wir inzwischen diese Annahme bestätigt gefunden und erfahren, dass Regelstörungen vor der Konzeption bestanden haben, und auch erwiesen, dass in der für die Entstehung der mandibulo-facialen Störungen kritischen Zeitspanne der 7. Embryonalwoche wiederholt „Hausmittel“ zur Fruchtabtreibung angewandt wurden und mehrfach Blutungen aus dem Muttermund beobachtet worden sind.

So sehr exogene Faktoren zu den Entstehungsbedingungen umschriebener Entwicklungsstörungen zu rechnen sind, aber auch eine Reihe Einzelbeobachtungen ohne fassbare ätiologische Anhaltspunkte mitgeteilt wurden, kann heute die Erblichkeit

der D. m. f. als erwiesen angesehen werden. Von den bisherigen Publikationen lassen die Angaben von BERRY, PIRES DE LIMA u. MONTEIRO, DEBUSMANN, MANHONEY u. PRICE, LEOPOLD, FRANCESCHETTI u. KLEIN, SANVENERO-ROSELLI, SCHACHTER u.a. eine Erbfolge unregelmässiger Dominanz ersehen. Dabei werden nach Berücksichtigung der bekannt gewordenen Mitteilungen Knaben häufiger befallen als Mädchen. Wesentlich erscheint die Feststellung, dass der Dominanzgrad in der Descendenz oft deutlich zunimmt. Wenngleich man die Dominanz nicht mehr als etwas Starres im Sinne der Präsenz-Absenz-Theorie von BATESON ansieht, sondern als etwas Relatives wertet, welches durch weitere im Gen gelegene Faktoren modifiziert werden kann, vermag doch gerade der Erblchkeitsfaktor die Erscheinungen der Polyphänie und die Labilität der Manifestationen bei dieser Genmutation zu erklären.

Die Steuerung solcher Genmutationen — von dem Verhalten anderer degenerativer Dysostosen hinreichend bekannt — stellt gewiss eine der rätselhaftesten Erscheinungen im Ablauf des Entwicklungsgeschehens dar, worüber sich bindende Gesetzmässigkeiten schwerlich aufstellen lassen. Überblickt man aber das vorliegende Krankengut von mandibulo-facialer Dysostose, so lassen sich innerhalb des Komplexes der mit D. m. f. koppelungsfähigen Anomalien trotz der Vielzahl möglicher Kombinationsformen einzelne Typen voneinander abgrenzen. Wir hatten Gelegenheit, die von FRANCESCHETTI, BROCHER u. KLEIN beschriebene „Dysostose mandibulo-faciale unilatérale“ zu bestätigen und haben bereits auf die mit den Kiefer-Gesichtsveränderungen aufgetretenen Wirbelanomalien hingewiesen. Bemerkenswerterweise betraf auch unser Fall die rechte Körperseite und verlief ohne Extremitätenbeteiligung. Diesem Typ sind Verläufe gegenüber zu stellen, wo mit den mandibulo-facialen Anomalien Störungen der Extremitätendifferenzierung (Aplasie beider Daumen, radio-ulnäre Synostose, NAGER) bezeichnenderweise ohne Wirbelbeteiligung gefunden werden.

An dieser Stelle erscheint eine Erweiterung des Blickfeldes auf genetisch nahestehende Zustandsbilder unerlässlich. Morphologisch gesehen lassen die Befunde der D. m. f. enge Beziehun-

gen zu dem in verschiedener Schwere vorkommenden KLIPPEL-FEIL'schen Syndrom erkennen. In extremen Fällen lässt diese Deformität eine Verschmelzung der gesamten Halswirbelsäule — den „bloc cervico-dorsale“ von FEIL — ersehen, wobei der sog. „proc. paramastoideus“ der D. m. f., eine knöcherne Verbindung der Schädelbasis mit den Querfortsätzen des Atlas, nur ein Teilsymptom einer umfassenderen Störung der Wirbelsäulenentwicklung darstellt. Als weitere Auswirkung der cervico-vertebralen Veränderungen sind Kyphosen und Skoliosen caudal gelegener Wirbelsäulenabschnitte und auf der Basis dieser Veränderungen entstehende Thoraxanomalien aufzufassen, wie sie beim KLIPPEL-FEIL häufiger, aber auch bei der D. m. f. mehrfach angetroffen werden (HERMANN, MANN, SCHACHTER, eigene Beobachtung). Neurologische Ausfälle finden sich mit Fehldifferenzierungen der oberen Extremitäten bei beiden Erkrankungen, wie auch Läsionen bestimmter Hirnnerven, welche sich vornehmlich mit fortschreitender Verknöcherung der Wirbelsäule ausbilden, beiden Dysostosen eigen sind.

Dieser vermutete Zusammenhang wird noch ersichtlicher, wenn man das Vorkommen von Gaumenspalten (PERRIER), „schiefen Augenspalten“ (PERROT u. BABAINANTZ) und Missbildungen der Ohren (INGELRANS u. PIQUET) mit KLIPPEL-FEIL'schen Deformitäten vergesellschaftet antrifft. Auch stellen die bei m. f. Dysostose erwähnten motorischen Innervationsstörungen des Sternocleidomastoideus für das Syndrom von KLIPPEL-FEIL keine Seltenheit dar, wie eine Übersicht von FEIL-LEBOURET u. FISCHER (100 Fälle) ersehen lässt. Das Auftreten bestimmter dem KLIPPEL-FEIL'schen Symptomenkomplex charakterisierenden Varietäten mit mandibulo-facialen Störungen lässt daher die Deutung zu, dass man es in solchen Fällen mit der Koppelung zweier degenerativer Zeichenkreise zu tun hat, Mechanismen, die für den Bereich der multiplen Abartungen nicht ungewöhnlich sind. Vom Standpunkt der vergleichenden Anatomie sind sodann einige Befunde der D. m. f. beachtenswert. Berücksichtigt man, dass das extremste Ausmass der m. f. Disproportionalität die bei Herbiforen häufigere Otocephalie darstellt, wie sie DEBUS-MANN in der Ascendenz einer mit m. f. Fehlbildungen behafteten

Familie fand, so erscheint der vorhandene Verschluss des äusseren Gehörganges (unsere Fälle 1, 2, 3) bei dieser Erkrankung in ein anderes Licht zu rücken. Während der Gehörgang des Menschen im Laufe der embryofetalen Entwicklung nur temporär verschlossen zu sein pflegt, um kurz vor der Geburt wieder eröffnet zu werden, erfolgt dies bei verschiedenen Quadrupeden erst nach der Geburt (ELLENBERGER, BAUM, PETRI). In gleicher Weise deutet auch das Auftreten eines Proc. paramastoideus, die Occipitalisation der Atlasquerfortsätze — besonders bei grossen Herbiboren entwickelt — darauf hin, dass es sich hierbei nicht schlecht-hin um eine ontogenetische Störung handelt, sondern dass Rückschlüsse der Phylogenese im Sinne „regressiver Varietäten“ vorliegen, die durch Otocephalie und Verschluss des Gehörganges nur unterstrichen werden können.

Die polyphänen genetisch oder umweltbedingten Störungen der mandibulo-facialen Dysostose können so erhebliche Grade annehmen, dass die Betroffenen nicht lebensfähig sind oder in den ersten Lebensmonaten zu Grunde gehen. Welches die Ursachen dieser Ereignisse sind, wissen wir nicht. Die Erbpathologie spricht von Letal- und Subletalfaktoren (LENTZ), welche allgemein durch wechselvolle Koppelung degenerativer Stigmata die Vitalität beeinträchtigen, mit Neigung zu Fehlgeburten und Frühsterblichkeit verlaufen und auch das Leben der ausgetragenen Früchte noch bedrohen. Die Wirksamkeit dieser Faktoren scheint im besonderen Masse die ersten Schwangerschaftsmonate zu betreffen wo nach der TSCHUPROW'schen Regel das Geschlechtsverhältnis („sex-ratio“) der Knaben zu Mädchen etwa 6 : 1 beträgt. Es ist somit die Annahme naheliegend, dass eine die embryofetale Frühentwicklung beeinträchtigende Schädlichkeit in einem höheren Prozentsatz Knaben befällt (wiewohl eine genaue Geschlechtsbestimmung in diesem Stadium auf Schwierigkeiten stösst) und die männliche Überzahl entwicklungsgestörter Individuen zu erklären vermag.

Die Grundfrage aller Krankheitsätiologie, ob Auswirkung krankhafter Erbfaktoren oder Folge exogener Einflüsse, berührt in besonderer Weise das Problem des Kymantodes. FRANKLIN P. MALL stellte fest, dass sich bei Fehlgeburten — besonders bei

jungen Exemplaren — Abweichungen geringen Grades finden, welche „als Vorläufer von erblichen Missbildungen“ angesehen werden müssen. Andererseits wissen wir aus der experimentellen Teratologie, dass auch auf Umweltschäden gesunde junge Eier mit der Ausbildung von Monstren reagieren, welche den Vergleichsbildern menschlicher Embryonen nicht nur ähnlich, sondern identisch sind (MALL). —

In eigenen Beobachtungen sahen wir die mit m. f. D. behafteten Kinder unter pneumonischen Erscheinungen im ersten Trimenon sterben; in der Geschwisterschaft fanden sich Früh- und Fehlgeburten, während das noch lebende Kind einer weiteren Beobachtung Entwicklungsrückstand und Schwerernährbarkeit zeigt.

Konstitutionspathologisch mag der Hinweis von Belang sein, dass in unseren Fällen die Väter der Probanden übereinstimmend eine ausgesprochene Dolichocephalie mit deutlicher Beeinflussung des Längen-Breitenindex und geringer Jochbogenbreite aufweisen und mit dem Schmalgesicht progene Unterkieferbeziehungen zeigen. —

Es erscheint abschliessend nicht unwesentlich, auf Grund des unverkennbaren Gesamthabitus der mandibulo-facialen Fehlbildungen die Selbständigkeit dieses Symptomenkomplexes zu betonen und diesen gegenüber ähnlichen degenerativen Dysostosen abzugrenzen. Differentialdiagnostische Schwierigkeiten können Fälle von Dysostosis cleido-cranialis (SCHEUTAUER-MARIE) Dysostosis cranio-facialis (CROUZON) und Akrocephalosyndaktylie (APERT) bereiten. Bei richtiger Bewertung der Abweichungen vom normalen Gesichtsaufbau wird man jedoch vor Verwechselungen sicher sein, solange man nicht einzelne Symptome überwertet oder aus dem Verband der im vorstehenden beschriebenen Symptomatologie löst. Selbst das von FRANCESCHETTI hervorgehobene Leitsymptom, der antimongoloide Verlauf der Lidachsen, ist davon nicht auszunehmen, da dieses häufiger in Verbindung mit einer Ausweitung des Augenabstandes (Hypertelorismus) beobachtet werden kann. Wir haben dieses Zeichen bei einer Reihe (mesodermaler) Konstitutionsanomalien gesehen [WEYERS (2)] und verweisen auf das gehäufte Vorkommen bei der CROU-

zon'schen Erkrankung. Wesentlich erscheint uns, das Verhalten des Stirn-Nasenfortsatzes zur Unterscheidung der D. m. f. von anderen dysosteogenetischen Störungen heranzuziehen. Während die aus diesem Segment hervorgehenden Gesichtsanteile (vordere Schädelgrube, Nasenskelett, Zwischenkiefer) bei der m.f. Dysostose ohne bemerkenswerte Deformierungen gefunden werden, weisen diese Regionen beim Mongolismus, bei der Dysostosis cleido-cranialis, Dysostosis cranio-facialis, Akrocephalosyndaktylie, Arachnodaktylie, u.a. hypoplastische Bildungsfehler auf. Hirndrucksymptome, die als Charakteristikum der CROUZON'schen Erkrankung und des Turricephalus bekannt sind, fehlen bei der D. m. f. auch im höheren Alter, wenngleich bei beiden Krankheiten accentuierte Impressiones digitatae, welche man gerne als Folge des Hirndruckes (SCHÜLLER) ansieht, auftreten. Dass dieses Zeichen beim mandibulo-facialen Syndrom ohne Anzeichen von Craniostenose gefunden wird, deutet darauf hin, dass die Wolkenbildung des Schädeldaches lediglich ein konstitutionelles Degenerationsmerkmal darstellt, welches Niveaudifferenzen der Lamellenarchitektonik in der Tabula interna bewirkt und als eine normale anatomische Variante (FÉNYES) aufzufassen ist.

Die klinische und pathologisch-anatomische Eigengesetzlichkeit der mandibulo-facialen Dysostose ist nach den obigen Darlegungen nicht zu bezweifeln.¹ Die Vitalität der Probanden lässt den Versuch therapeutischer Eingriffe zur Behebung der entstehenden Physiognomien wünschenswert erscheinen. Richtungsweisende Wege haben hierzu Kieferchirurgen verschiedener Nationen (JOHNSTONE, SANVENERO-ROSELLI, STRAITH u. LEWIS) gewiesen, um durch operative Korrektur der Kiefer- und Orbita-defekte sowie der Ohrdeformitäten (PEER u. AUFRICHT, s. hierzu SCHUCHARDT) das Los ihrer Träger zu erleichtern. Die Ausgangsbedingungen zu einer operativen Mobilisation der verkümmerten akralen Gesichtsbezirke dürften umso günstiger sein, als es sich nicht um geschädigtes und strukturell verändertes Gewebe handelt, das in der Regel den grössten Anteil plastischer Rekonstruktionsversuche ausmacht.

¹ In einer interessanten Studie hat H. GÜNTHER (Virchows Archiv: 319: 282, 1950) die syndromale Koppelung von Mikrognathia inferior und Deformationen der Ohrmuscheln erwähnt und nach dem ersten Beschreiber (1847) als „Thomsonkomplex“ bezeichnet.

Zusammenfassung

1. An Hand eigener Beobachtungen wird auf eine Anlagestörung des Kiefer-Gesichtsbereiches eingegangen, welche als ein Differenzierungsmangel bestimmter, der ersten Kiemenfurche anliegenden Gewebsareale anzusehen ist, unter einem charakteristischen Erscheinungsbild verläuft und von FRANCESCHETTI u. ZWAHLEN (1944) unter der Bezeichnung „Dysostosis mandibulo-facialis“ zusammengefasst wurde.

2. Der mandibulo-faciale Symptomenkomplex lässt eine ausgesprochene Organdisposition erkennen und tritt mit Makrostomie, Mikrotie und Mikrognathie sowie Defekten der temporalen Augenhöhlenwand und ihrer Weichteilbedeckung in Erscheinung. Letztere Bildungsfehler sind im wesentlichen durch eine Hypoplasie der Jochbeine bedingt und führen zu einem antimongoloiden Verlauf der Lidachsen.

3. Ausser den Veränderungen des Gesichtskeletts werden Thoraxanomalien, Lungendysplasien, Wirbelsäulen- und Extremitätenmissbildungen beobachtet, welche über die umschriebene Dyskranie auf eine Generalisationstendenz der Fehlbildungen im mesodermalen Gewebsbereich schliessen lassen.

4. Es gibt Standardtypen mit der Vollzähligkeit aller genannten Symptome, „formes frustes“ und Halbseitenlokalisationen des mandibulo-facialis Prozesses, als dessen extremste Grundform die bei Quadrupeden häufigere Otocephalie anzusehen ist. In belasteten Sippen treten mit den klinischen Vollbildern Abortivformen auf; jedoch wird auch ein sporadisches Vorkommen beobachtet.

5. Klinische und pathologisch-anatomische Befunde deuten darauf hin, dass sich diese Erkrankung um die 7. Fetalwoche manifestiert, Beziehungen zum KLIPPEL-FEIL'schen Symptomenkomplex aufweist, im übrigen aber als ein selbständiger Biotypus gegenüber anderen degenerativen Dysostosen sicher abzugrenzen ist.

WEYERS, H.: *Mandibular facial dysostosis, a new syndrome of "multiple degeneration."*

1. On the basis of his own observations the author describes a hereditary perturbation of the jaw and face area, which is to be regarded as a differentiation defect of certain zones of the tissues of the first branchial cleft, and shows in its development a characteristic picture which has been described by Franceschetti and Zwaalen (1944) under the designation of "dysostosis mandibulo-facialis."

2. The complex of mandibular facial symptoms is recognisable by a pronounced disposition of the organs and is manifested by macrostomia, microtia and micrognathia, as also by defects of the temporal orbit walls and their soft tissue covering. These deformations are chiefly caused by

hypoplasia of the zygomatic bone and lead to an anti-mongolian course of the eyelid axis.

3. Besides the changes in the bone of the face, there are observed anomalies of the thorax, dysplasia of the lungs, malformity of the spinal column and the extremities, which indicate a generalisation tendency to malformation of the mesodermal tissue in addition to the above described cranial abnormalities.

4. There are standard types showing all the above symptoms, "formes frustes" and one-sided localisations of the mandibular facial process, as well as the extreme basic form which is to be regarded as frequent of otocephalia in quadrupeds. In cases with hereditary taint abortive forms also occur in conjunction with the full clinical picture, but sporadic cases have also been observed.

5. Clinical and pathological anatomical findings suggest that this disease manifests itself around the 7th week of gestation, that it is related to the Klippel-Feil complex of symptoms, but that it can be distinguished in general as a separate biotype from other degenerative dysostoses.

WEYERS, H.: *La 'dysostose mandibulo-faciale,' nouveau syndrome de «malformations multiples».*

1. Sur la base de propres observations l'auteur traite une perturbation héréditaire de la partie de la mandibule faciale, qui doit être considérée comme un défaut de différenciation de certaines zones de tissus voisines du premier sillon branchial et présente dans son développement une image de symptômes caractéristiques, réunie par Franceschetti et Zwahlen (1944) sous la dénomination de «Dysostosis mandibulo-facialis».

2. L'ensemble des symptômes mandibulo-faciaux manifeste une disposition prononcée des organes et se présente accompagné de macrostomie, de microtie et de micrognathie ainsi que de défauts des parois temporales des orbites et de leur recouvrement de tissus mous. Ces derniers défauts de formation sont essentiellement dus à une hypoplasie des apophyses zygomatiques et mènent à un développement antimon-goloïde des axes des paupières.

3. Outre les changements du squelette du visage, on observe des anomalies du thorax, des dysplasies des poumons, des déformations de la colonne vertébrale et des extrémités, qui, par l'intermédiaire de la dyscranie décrite antérieurement, permettent d'arriver à la conclusion que l'on se trouve en face d'une tendance de généralisation des déformations de la superficie mésodermale des tissus.

4. Il existe des types généraux qui présentent la totalité des symptômes mentionnés, des «formes frustes» et des localisations dans l'un des côtés du processus mandibulo-facial, dont l'otocéphalie, plus fréquente chez les quadrupèdes, peut être considérée comme la forme pri-

mitive la plus extrême. Chez les familles affectées héréditairement, on trouve conjointement à des images cliniques complètes des formes abortives; cependant, on a aussi observé des cas sporadiques.

5. Les signes cliniques et pathologo-anatomiques indiquent que cette maladie se manifeste vers la septième semaine foetale, qu'elle montre des rapports avec l'ensemble des symptômes de Klippel-Feil, mais que, pour le reste elle doit être nettement séparée des autres dysostoses dégénératives, comme type biologique indépendant.

WEYERS, H.: *La «dysostosis mandibulo-facialis»; nuevo síndrome de malformaciones múltiples.*

1. Sobre la base de observaciones propias, el autor trata una perturbación hereditaria de parte de la mandíbula facial, que debe ser considerada como un defecto de diferenciación de ciertas zonas de tejidos vecinos del primer surco branquial y que en su desarrollo ofrece una imagen de síntomas característica, reunida por Franceschetti y Zwahlen (1944) bajo la denominación de «dysostosis mandibulo-facialis».

2. El conjunto de síntomas mandíbulo faciales denuncia una disposición marcada de los órganos y se presenta al mismo tiempo que la macrostomia, la microtomia y la micronatía, así como defectos del tabique temporal de las órbitas y de su recubrimiento de tejidos blandos. Estos últimos defectos de formación son en su mayoría debidos a una hipoplasia de huesos cigomáticos y conducen a un curso antimongoloide de los ejes de los párpados.

3. Además de los cambios del esqueleto de la cara se han observado las anomalías del torax, displasias de los pulmones, deformaciones de la columna vertebral y de las extremidades que, pasando por la discrania antes descrita, permite llegar a la conclusión de que nos encontramos en presencia de una tendencia de generalización de las deformaciones de la superficie mesodermal de los tejidos.

4. Hay tipos generales que presentan la totalidad de los síntomas enumerados, las formas frustas y localizaciones en uno de los lados del proceso mandíbulo facial, como cuya forma primitiva más extremada puede ser considerada la otocefalia bastante frecuente en los cuadrúpedos. En las familias hereditariamente afectadas se encuentra también en formas abortivas al lado de las imágenes clínicas enteramente desarrolladas; sin embargo no se han observado casos esporádicos.

5. Las señales clínicas y patológico-anatómicos indican que esta enfermedad se manifiesta aproximadamente alrededor de la séptima semana fetal, que muestra relaciones con el conjunto de síntomas de Klippel-Feil pero que, por lo demás, debe estar separada netamente de las otras disostosis degenerativas como un tipo biológico independiente.

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CASE REPORTS

Gargoylism, *Forme Fruste*

by

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Gargoylism (dysostosis multiplex, lipochondrodystrophy, osteochondrodystrophy) is also called Hurler's syndrome after HURLER who described 2 cases in 1919. Previously, however, the syndrome had been observed in 1917 by HUNTER, and as early as 1900 by Dr. John Thomson of the Royal Edinburgh Hospital who named it "Johnny McL...s disease" after the first patient. Among Johnny's 8 siblings Dr. Thomson found 2 similar cases in 1908 and 1913. All three cases were later published by HENDERSON (1940).

From Scandinavia the disease has been reported by ARNOLDSSON & NORDENSSON (1 doubtful case), NJAA (6 related boys), and LUNDSTRÖM (3 boys). In 1947, the latter author reviewed the published cases, numbering 80. Since then, a few cases have been added each year (inter alia 13, 21, 22).

The syndrome is motley and varied, but the cardinal symptoms are dwarfism, imbecility, bony deformities, corneal clouding, and hepatosplenomegaly. For details the reader is referred to 2, 9, 11, 15, 17, 18, 22, and 23.

As a rule the disease is classified with the lipoidoses (2, 5, 13) because of an unknown intracellular and perivascular deposition of lipid-like substances in the brain, pituitary body, lymph nodes, lungs, heart, thymus, spleen, testes, and cornea. STRAUSS *et al.*, however, found increased lipoids only in the lymph nodes in their case. Being unable to identify this deposition as cerebroside, cholesterol, or phosphorus lipoids, they distinguish the disease from lipoidoses. They advance the theory that the disease involves primarily the connective tissue, giving rise to shrinkage which results in the deformities. It is worth mentioning that involvement of the adrenals has not been found yet (2, 22).

The disease has a tendency to be familial, occurring chiefly in boys (17, 22). LAHEY *et al.* have observed a case occurring in a Negro. It has been reported in identical twins (19) and in one of two dissimilar

twins (15). The symptoms usually set in before the end of the first year of life, but STRAUSS *et al.* have described a boy who remained normal until the age of 9 after which he developed the typical symptoms. Most of the patients succumb to respiratory tract infections or heart failure before the age of 10. The case of STRAUSS *et al.* reached the age of 29. The secondary sex characters fail to appear, and the condition is accompanied by amenorrhoea, and absence of spermiogenesis (2, 5, 9, 11, 16, 20, 22).

The following is a report of a case of dwarfism which was found difficult to classify, but which appears to fall into the group of gargoylism.

A boy, aged 10, admitted to the Medical Department of the County Hospital in Herning (No. 1372/49) from Jan. 24 to Feb. 15, 1947, and from Nov. 16 to 19, 1949. Admission diagnosis: Nanism.

The patient is the second of five children. His siblings are healthy and of normal stature. In addition, there had been a sister, younger than the patient, who died at the age of 2 1/2, presumably from pneumonia. She was small, walked and talked at 1 and 1 1/2 years respectively, and was reported to have shown prominence of the forehead. The anterior fontanelle was stated to have been about 5 cm immediately before death. There were two normal siblings between the patient and this sister.

Parents are healthy and not aware of dwarfism having occurred in the family.

Born at full term after a normal labour, birth weight 2 500 g. Presentation unknown. Received cod-liver oil in the winter months from the age of 6 months. Walked at less than 1 year and talked earlier than his siblings. Apart from whooping cough and measles about the age of 7, he had been healthy. No known cases of tuberculosis in the environment. Admitted to Herning Hospital at the age of 6 months, because he failed to grow and because of the large size of his head. Diagnosis: Hydrocephalus.

He is the best at school and gets on well with his class mates without being troubled by his small stature.

Lately he had been complaining of headache when reading in artificial light. Vision otherwise normal. Appetite normal, does not suffer from thirst. All functions normal.

Clinical findings: Height 104 cm, weight 19.3 kg, circumference of head 55 cm (normal values 137 cm, 32 kg, 52 cm (Monrad)). Anterior fontanelle open, about 7 × 12 cm, the ends continuing as broad sutures. As compared with the cranium on the whole, the calvarium is very large and the tubera frontalia very prominent. Depressions at the temples. The shape of the skull is dolicocephalic. Apart from the open sutures, the cranium gives the impression of being very solid. Eyes deep-set,



Fig. 1 and 2.

jaws well-developed and maxillary processes prominent. Mandible receding.

The shape of the chest is normal, but the sternal ends of the ribs project, suggesting Harrison's groove. Lumbar lordosis very marked. The patient is a very muscular boy, and the subcutaneous tissue is more marked than normal (Fig. 1 and 2). Hands and feet are short and remarkably broad, the distal phalanges particularly short and clubbed (Fig. 3), without, however, the nails being particularly thick or broad. The skin of the fingers is coarse and wrinkled, but otherwise normal.

Mentally, the patient appears to be perfectly normal.

Eyes: pupils normal. No injection, refracting media clear; iris, lens, vitreous body, and ophthalmoscopic findings normal.

Ear, nose, and throat normal.

Teeth very close together, slightly overriding.

Subcutaneous lymph nodes normal.

Auscultation of heart and lungs normal.



Fig. 3.

Abdomen: No hepato-splenomegaly. No umbilical hernia. Hernial orifices normal.

External genitalia normal.

Limbs: Of normal length compared with the trunk. No limitation of the mobility in the joints. Reflexes normal.

Laboratory tests: Hb. 91 %, differential count normal. No abnormal granulation of the white blood cells. Sedimentation rate 2 mm. Moro and Mantoux reactions negative. Urine: no protein, no sugar. Concentration test: specific gravity 1030. Total cholesterol 148 mg %. Serum phosphorus 4.3 mg %. Fasting blood sugar 78 mg %. Glucose tolerance test: Blood sugar at the end of 1 hour, 164 mg %, (urine showed no sugar), at the end of 2 hours 106 mg %, at the end of 3 hours 86 mg %. Serum calcium 11.6 and 11.9 mg %. Blood pressure 105/80. Sternal bone marrow showed nothing definitely abnormal; the granules of the white blood cells were normal.

X-ray examination (Fig. 4 and 5): Marked enlargement of the theca cranii and deficient fusion of the bones (development corresponds approximately to that in the 7th—8th foetal month). Several cm's diastasis between the sutures, fontanelles very large and broad. Tubera frontalia prominent. Numerous wormian bones. Sella turcica about 6 × 8 mm (normally 9.3 × 9.9 mm at the age of 10—13). Lower jaw strangely flattened without normal angulation. Facial bones otherwise small, but normal.



Fig. 4.

Vertebral column straight, the vertebral bodies small, but of normal shape and ossification. Spondylolisthesis, there being a couple of cm between the sacral bone and the lumbar column. Some fusion of the last lumbar and first sacral segment.

The limbs are rather slender, fingers and toes small and stumpy, the distal phalanges not normally developed, showing deficient ossification. Otherwise, the nuclei of the bones are normal. On the right foot, false joints in the middle of the 2nd and 3rd metatarsals. Epiphyses normally developed.

In addition to the changes mentioned above, there was pronounced universal osteosclerosis. In the upper part of the femora, the cortex is so thick as to obliterate the medullary cavity almost entirely. The X-ray appearance of the cranial bones is also very hard and dense.

When admitted again, about 22 months later, his height had increased by 6.5 cm up to 110.5 cm, the weight by 3.2 kg up to 22.5 kg, and the circumference of the head by 1 cm up to 56 cm. Otherwise, the findings are the same, and there are no subjective complaints.



Fig. 5.

Summary of the Case: A boy, aged 10 years, showing proportioned dwarfism, monstrous shape of the skull, open fontanelles and broad sutures, flattened mandible, and depressions at the site of the temporal bones. Hands and feet stumpy, the distal phalanges clubbed. Skin of the fingers coarse and wrinkled. X-ray showed pronounced osteosclerosis in the metaphyses, vertebral bodies and skull; distal phalanges small showing deficient ossification. Intelligence normal. In 22 months, the height had increased by 6.5 cm, the weight by 3.2 kg, and the circumference of the head by 1 cm.

Discussion. The various forms of dwarfism are divisible into the following categories (FAURBYE):

(A) Genuine dwarfism.

(B) Secondary dwarfism, i.e., cases in which an originally normal height is reduced to a dwarfish stature, such as in Pott's disease resulting in hunchback.

(A) may be subdivided as follows:

- (1) Inherited and constitutional factors: Dwarf races (pygmies, primordial dwarfism).
- (2) Congenital bone diseases: Achondroplasia, micromelia.
- (3) Other congenital lesions: Mongolism, congenital heart disease.
- (4) Chronic infectious diseases: Tuberculosis, syphilis.
- (5) Renal disorders: Renal rickets.
- (6) Deficient absorption of food: Coeliac disease, helminthiasis.
- (7) Deficient ingestion of food: Starvation, avitaminosis, mineral deficiency.
- (8) Endocrine disorders: Abnormalities of the pituitary, congenital myxoedema, precocious puberty, Addison's disease, endemic cretinism.
- (9) Atypical varieties which cannot be classified and which are often combined with endocrine disorders: Gargoylism, Morquio's disease.

In this case, the first seven varieties mentioned may be disregarded. The patient exhibited no signs of congenital heart disease, chronic infectious diseases, renal or intestinal disorder. Neither were there any signs of deficient ingestion of food.

The fairly proportioned appearance of the patient does not remind one of the characteristic aspect of the achondroplastic dwarf whose dwarfism is due primarily to the short and curved extremities. On the X-ray film, the limbs in achondroplasia are stumpy with irregular epiphyses and a thin cortex.

Nor was there any resemblance to myxoedema, which often is confused with gargoylism, and the serum cholesterol was perfectly normal.

Neither were there deformities of the vertebral column, pelvis, or limbs resulting from rickets.

For some time the possibility of a pituitary origin was considered (cf. the small sella), perhaps due to hydrocephalus. Proportioned pituitary dwarfs, however, invariably show genital hypoplasia which was not seen in this case. In the glucose tolerance test they show marked hyperglycemia which also did not occur in our patient. Hands and feet are usually more slender, and X-ray shows osteoporosis in pituitary dwarfs whose appearances are, on the whole, unlike that of our patient (cf. Figs. 3—4—5).

Neither did the syndrome resemble Morquio's disease, the most outstanding signs of which are the nearly complete absence of a neck, the deformity of the chest, and the pronounced valgus deformity of the knees which practically prevents the victims from walking.

In addition to the dwarfism, the changes which suggest gargoylism are the large, monstrous head with open sutures, the stumpy hands and

feet with coarse, wrinkled skin, and clubbed distal phalanges showing deficient ossification, and, furthermore, osteosclerosis.

Normal intelligence is no rare finding in these patients. LIEBENAM'S 13-year-old patient, NONNE'S 16-year-old twins and 9-year-old patient (3 siblings) were among the best at school. ELLIS' one patient, LANGE'S two and STRAUSS *et al.*'s patients were all of normal intelligence.

Absence of corneal clouding has been reported in 20 % of the cases (17). NJAA has set up a special variety of familial gargoylism without corneal clouding, found only in boys and characterized by sex-linked, recessive heredity. This variety has so far been found in only one family. Our patient cannot fall into this group, since the other presumed case among the family occurred in a girl and since the disease should in that case be manifest in the father, but this was not so.

No, or only slight, hepato-splenomegaly has been reported in several instances (3, 2, 4).

It is of course difficult to say anything about the prognosis in this case, but the former fruste patients appear to live longer than the others (HENDERSON). Treatment with growth hormone has been considered, but the idea has been abandoned, since pituitary hormone as well as thyroid hormone have proved ineffective in previous cases (2, 11, 15, 17, 18, 19).

Addendum

Since this was written, the patient has got a little sister who was admitted to the department at the age of 5 months. Her appearance is very much like her brother's and therefore seems worthy of brief mention.

Height 55 cm, weight 4 450 g, circumference of skull 40.5 cm, circumference of chest 35 cm, length of lower limbs 24 cm and of upper limbs 19 cm.

Apart from the facial bones, the head is remarkably large and of striking shape. The frontal and parietal bones are prominent. The anterior fontanelle is large and the sutures open. The sagittal suture is palpable from the middle of the forehead as far as the posterior fontanelle which is 1×2 cm. The sutures issuing from the latter are also open. Sternum slightly depressed, but no other deformities of the chest or vertebral column.

All the fingers and toes are of a peculiar shortness and clubbed. The skin over the tips is swollen and wrinkled. Nails thin and concave with frayed edges.

At her present age it is impossible to state with certainty whether the condition is more abortive or incomplete in her case than in that of her brother.

Summary

After briefly reviewing previously reported cases of gargoylism, the writer describes a 10-year-old boy of normal intelligence showing proportioned dwarfism, a large monstrous head with open sutures and fontanelles, stumpy hands and feet with clubbed distal phalanges, and a coarse, wrinkled skin on the fingers. X-ray examination showed well-marked osteosclerosis of the skull, vertebral column, and metaphyses, deficient ossification in the distal phalanges. The diagnosis is discussed, and the case is interpreted as one of gargoylism (forme fruste).

K.-E. SJÖLIN: *Gargoylism, Forme Fruste.*

Après une courte revue des cas de gargoylisme antérieurement rapportés dans la littérature, l'auteur décrit celui d'un garçon de 10 ans, d'intelligence normale, présentant un nanisme bien proportionné, avec une macrocéphalie importante, persistance des fontanelles et sutures ouvertes, des mains et des pieds trapus avec phalanges distales enflées et une peau ridée et rugueuse au niveau des doigts. L'examen radiologique montra de l'ostéosclérose du crâne, de la colonne, des métaphyses et des déficiences de l'ossification dans les phalanges distales. Le diagnostic est discuté et le cas est considéré comme une forme fruste de gargoylisme.

K.-E. SJÖLIN: *Gargoylismus, Forme Fruste.*

Nach kurzer Übersicht über früher berichtete Fälle von Gargoylismus, beschreibt der Autor einen 10 Jahre alten Knaben von normaler Intelligenz. Er zeigte proportionierten Zwergwuchs, einen grossen, monströsen Kopf mit offenen Nähten und Fontanellen, plumpe Hände und Füsse mit breiten distalen Phalangen, derbe faltige Haut an den Fingern. Die Röntgenuntersuchung zeigte typische Osteosclerosis des Schädels, der Wirbelsäule und der Metaphysen; mangelhafte Ossifikation an den distalen Phalangen. Die Diagnose wird diskutiert und der Fall wird interpretiert als Gargoylismus (forme fruste).

K.-E. SJÖLIN: *Gargolismo. Forma Frustra.*

Después de haber trazado un breve resumen de casos de gorgolismo descritos anteriormente, el autor describe a un niño de 10 años de inteligencia normal, que muestra un enanismo proporcionado, una gran cabeza monstruosa con suturas y fontanelas abiertas, manos tozas y pies con falanges distales ensanchadas, y piel tosca y arrugada sobre los dedos. El examen con los rayos X mostró una osteoesclerosis bien marcada del cráneo, columna vertebral y metafises, y deficiente osificación en las falanges distales. Se discute la diagnosis y el caso se interpreta como uno de gorgolismo (forma frustra).

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Aureomycin Treatment in a Newborn Premature Infant with *Bacillus Coli-Meningitis*

by

GUNNAR LAURELL, J. HENNING MAGNUSSON and BIRGITTA WERNER

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Coli-meningitis in young infants is not a very common disease. A survey of the more important papers on the subject was published by MAGNUSSON, GILLE and LAURELL in 1949 (4). The prognosis has up to recently been bad. With the new antibiotics now in use the chances of successful treatment have increased. A report has recently been published from the Sachs' Hospital for Children describing a case of *coli-meningitis* that was treated successfully with streptomycin. Aureomycin, however,

would in several ways seem to be a better drug to use in the treatment of infections caused by gram-negative bacteria. Only two cases have as yet been placed on record showing the effects of aureomycin in newborn infants with meningitis (5). In one case the infecting organism was *B. pyocyaneus* and in the other a coliform bacillus (*Aerobacter aerogenes*). In the present paper, a case of meningitis treated with aureomycin will be described. Points of interest in connection with the case are that the infant was prematurely born, and also that prior to the meningitis it had had severe scleroedema which was treated with vitamin E.

The patient was a boy, born prematurely on April 8, 1950. He weighed 1750 g at birth and was transferred to this hospital immediately because of his prematurity. The mother, a 34 year old primipara, had had moderately severe albuminuria during the final weeks of her pregnancy but otherwise it had been normal. On admission, the patient appeared to be a typical premature infant without any particular signs or symptoms. One and a half days later, however, scleroedema appeared on his legs. Within twenty-four hours it had spread all over the lower half of his body below the level of the umbilicus, and extended up his back between the shoulder-blades and out to the left side of his neck. The edema was so hard that the child was as stiff as a celluloid doll and was unable to relax his muscles. Vitamin E therapy (Ephlynal Roche) was instituted three days after birth, 30 mg being administered intramuscularly on the first day, 2 doses of 15 mg each, orally, for two days, and 7 mg twice daily for a further two and a half days. On the fourth day of life no edema remained on the neck, and twenty-four hours later the whole condition had subsided noticeably. A small edematous area still persisted on the thighs when the treatment was discontinued because of loss of weight, but this disappeared spontaneously without any further measures being taken.

After this, the infant appeared to be quite well for about a day; then his temperature rose to 38° C without there being any other signs of infection. His temperature fell after the heating in the incubator had been regulated, but it rose again, to 39° C, ten days after birth. The infant seemed irritable when it was touched and it looked slightly pale, but there was no neck stiffness and no increase in the tension of the fontanel. Lumbar puncture, however, yielded an extremely cloudy fluid showing abnormally high protein values and 3 140 leukocytes of which 1 640 were polymorphonuclears. In addition to penicillin therapy, which had been given as a prophylactic measure, treatment with streptomycin and a sulfonamide (Elkosin) was started. Heparin was administered intravenously for twenty-four hours because of the strong precipitation of protein in the cerebrospinal fluid. Breast milk was given as food. Additional fluid was injected subcutaneously (Aminosol-glycose, Darrow's solution). The bacteriological examination showed coliform bacilli in

Table 1.

Examinations of cerebrospinal fluid.

Age in days	Appearance of fluid	No. of cells per mm ³				Protein		Culture of fluid
		Leuko-cytes	Poly-morphs	Mono-nuclears	Erythro-cytes	Pandy	Nonne	
10	Yellow, turbid	3,140	1,640	1,500	850	+++	++	Heavy growth of <i>E. coli</i>
12	Pale, slightly turbid	479	249	230	110	++	++	No growth
20	Colourless, clear	278	16	262	19	++	+	—
24	Bloody	—	—	—	—	—	—	No growth
28	Bloody	—	—	—	—	—	—	No growth
62	Colourless, clear	18	0	18	97	(+)	(+)	No growth

pure culture in the cerebrospinal fluid. As the strain proved to be extremely sensitive to aureomycin, this was substituted for the earlier forms of therapy. It was administered orally for the first time on the eleventh day of life. For the first three days the daily dose given was 70 mg per kg of body weight; it was then reduced to 35 mg per kg. Vitamin B was given orally in conjunction with the aureomycin treatment.

After three days' treatment (13 days after birth) the temperature had returned to normal and the patient began to gain weight. Examination of the cerebrospinal fluid twelve days after birth showed a count of 479 leukocytes, 279 of which were polymorphs and cultures were sterile. The infant's general condition was now satisfactory, although he was slightly apathetic and showed a tendency to vomit (an effect of the aureomycin). Twenty days after birth Pandy's and Nonne's tests were still positive and the cell count was 278, with only 16 polymorphs.

While convalescent, the patient lay for one week with his head bent slightly backward; there was no neck stiffness, however, and the head subsequently resumed its natural position. Fairly severe anemia developed during the course of the infection, but this responded well to iron therapy. The aureomycin treatment was withdrawn after three weeks. At an examination of the cerebrospinal fluid, roughly two months after the onset of the illness, slight traces of protein and 18 mononuclear cells were observed. This finding is probably to be explained as being a reac-

tion to the bleeding from the needle wound that had occurred when the last two samples were taken. In other respects the infant's general condition was satisfactory at this stage. The weight increase was good. The anterior fontanel showed normal tension. The head circumference was normal — 38.5 cm at the age of 3 months. Ophtamoscopic examination showed normal conditions. Mentally the infant developed well; at 3 months of age he smiled for instance adequately, followed moving objects with his eyes and held his head steady. No events of interest were recorded up to the age of 4 months, during which time he had been kept under observation.

Bacteriological Findings

A gram-negative organism was isolated from the cerebrospinal fluid in a culture made during the acute stage of the illness. Judging by its morphological and cultural characteristics it was a coliform bacillus. Its biological reactions are shown in table 2.

Table 2.
Biochemical properties of test strain.

Strain	V. P.	Methyl red	Indole	Hemolysis	Citrate
10,243	—	+	+	—	—

10,243 isolated from cerebrospinal fluid.

It would seem that the strain belonged to the *Escherichia coli* group of coliform bacteria.

Serology

The strains were also examined from the aspect of their serological properties, the method of examination used being that elaborated by KAUFFMANN and VAHLNE (2, 6). The strain was found to be non-motile and to lack capsular antigen. The somatic antigen component did not belong to any of those included in KAUFFMANN and VAHLNE's classification of antigens, but was found, instead, to be identical with a strain that had been observed by LAURELL (3) in an investigation¹ into the flora of the respiratory tract in young infants. About 25 strains that had been isolated from the infant's respiratory tract and faeces, and from the

¹ This investigation was carried out at the Sachs' Hospital for Children during the years 1947 and 1948.

mother's faeces, were also examined serologically. The same type of strain was demonstrated in the infant's faeces as had been isolated from its cerebrospinal fluid. Using the strain from the cerebrospinal fluid as antigen, a "coli-Widal" test was carried out against serum taken from the infant 2, 10 and 17 days after birth. No agglutination was observed.

Discussion

The present report refers to an infant admitted to the hospital because of prematurity. During the first few days of life a dangerous degree of scleredema developed. According to GERLOCZY (1), who, in 1949, published a description of 38 cases of scleredema in premature infants, resolution of the edema and increased diureses can be achieved with vitamin E in these infants. Treatment with this vitamin was instituted immediately in our case, apparently with good effect. The edema decreased in extent and had disappeared completely after a few days' treatment. Ten days after birth the patient became ill with meningitis and an abundant growth of coliform bacteria was obtained from the cerebrospinal fluid. These forms of meningitis are not a common occurrence in children, and there are few reports about the treatment of such cases. A description of one case that was successfully treated with streptomycin has already been published from the Sachs' Hospital for Children, and the effects of aureomycin treatment in another case has appeared in J. A. M. A., in 1950. In the case under discussion in the present paper streptomycin was tried first, and then, as the strain proved to be very sensitive to aureomycin, this was substituted on the second day of illness. The effect was good, the infant soon losing all clinical signs of the disease. The serological analysis showed that strains identical with those in the cerebrospinal fluid could be isolated from the intestines of the child but not from its throat, or from the mother. No agglutinins against the strain were found in serum from the patient, but this was not surprising, in view of the short clinical course.

Summary.

A report is given of a case of acute meningitis caused by coli bacilli in a newborn premature infant with scleredema. The coli strain was isolated. It proved to be very sensitive to aureomycin, and was also studied from the aspect of its serological properties. The infant was treated with aureomycin with good clinical effect.

G. LAURELL, J. H. MAGNUSSON et B. WERNER: *Traitement par auréomycine d'un cas de méningite coli-lacillaire chez un nouveau-né prématuré.*

Il est rapporté un cas de méningite aiguë à coli bacilli chez un nouveau né prématuré et présentant du scléroedème. La souche fut isolée. Elle se révéla sensible à l'auréomycine, et fut étudiée également sous l'angle de ses propriétés sérologiques. L'enfant fut traité par l'auréomycine.

G. LAURELL, J. H. MAGNUSSON und B. WERNER: *Aureomycinbehandlung von Coli-Meningitis bei einem Frühgeborenen.*

Es wurde berichtet über einen Fall von akuter Meningitis verursacht durch Bacterium Coli bei einem frühgeborenen Kind mit Scleroedem. Der Colistamm wurde isoliert. Es bestand eine grosse Empfindlichkeit gegen Aureomycin und der Stamm wurde untersucht hinsichtlich seiner serologischen Eigenschaften. Das Kind wurde mit Aureomycin behandelt

G. LAURELL, J. H. MAGNUSSON y B. WERNER: *Un caso de coli-meningitis en un niño prematuro recién nacido tratado con aureomicina.*

Se describe un caso de meningitis aguda, causada por gérmenes coli, en un niño prematuro recién nacido con escleredema. La cepa coli fué aislada. Esta se mostró muy sensible a la aureomicina y también se estudió desde el aspecto de sus propiedades serológicas. El niño fué tratado con aureomicina.

Addendum: The infant returned, however, later blind and mentally defect. During the first time at home he had been normal. After 1 month it had, however, become gradually more and more difficult to come in contact with him. He no longer smiled as before when spoken to. Later on he got incoordinated ocular movements. At 7 months of age convulsions started. The head circumference was still normal, 43.5 cm at the age of 8 months, and the fontanel, 1 × 1 cm, did not show any increased tension. X-ray examination showed normal configuration and size of the skull, and no separation of the cranial sutures. The ventriculogram, however, showed internal hydrocephalus combined with cortical atrophy. At repeated ophtalmoscopic examinations no abnormal condition could be found, but no retinal function could be demonstrated in the electroretinogram. The infant died in pneumonia nine months old. At autopsy the X-ray findings were confirmed, internal hydrocephalus and cortical atrophy being revealed. Whether the lesions were caused by the passed meningitis or not could not be established. No pathological changes definitely due to it could be observed.

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FROM CHILDREN'S HOSPITAL OF THE UNIVERSITY OF ATHENS,
ATHENS, GREECE. CHIEF: PROF. DR. C. CHOREMIS.

Studies on the Diastatic Activity of the Blood in Children

by

JOHN B. NICOPoulos

Previous quantitative studies of the concentration of diastase in the blood have shown that the values obtained are remarkably constant under similar circumstances. Early investigators of diastatic activity of the blood of normal children found variations with age being almost absent at birth, rising rapidly during the first year of life and then increasing gradually until puberty (1). This rise in the blood diastase is parallel with the secretion of diastase by the salivary glands and pancreas (1). It has also been noted that blood diastase levels have been reduced to half the normal by pancreatectomy (2). In pathological conditions involving the salivary glands and pancreas, such as mumps and pancreatitis, the level of diastase of the blood has been found markedly increased (3). From these and other observations, investigators have concluded that the diastase found in the blood is primarily derived from the secretions of digestive glands and is absorbed from the small intestine. However, VON EULER and OPPENHEIMER (4) have demonstrated the presence of diastase in liver, heart, muscles, adrenal, skin and testicular tissues and these must contribute to the level of diastase in the blood. Correlation studies on diastatic activity of the urine have shown a direct relationship to the level of diastatic activity of the blood, indicating that the urine is the normal pathway for the excretion of diastase from the blood (5).

Studies of diastatic activity of the blood in many pathological conditions in children have revealed a significant decrease of diastase in severe infectious diseases and many forms of malnutrition (6). This decrease in diastase levels has been attributed to a decrease in the functional activity of the exocrine glands producing diastase or to a decrease in intestinal absorption. It seems possible, however, that this decrease may not only be due to a decrease in the function of these organs, but may also be due to a disturbance of the intermediary metabolism of the many other tissues which produce diastase.

To study this question we have examined the variations in the diastase levels of blood with variations in blood chloride levels. This method was chosen because of the well known fact that the presence of chloride ions is necessary for the activity of diastase found in the salivary and pancreatic secretions (7). The procedure followed was to determine the level of diastatic activity of normal children and the same children after they have been rendered hypochloremic by dietary control. The third phase of this investigation was to determine the diastatic activity under pathological conditions, where hypochloremia is known to exist.

Procedure

The diastatic activity of the blood was determined by the method of CHROMETZKA and ERLEMANN (8). This is based upon the determination of the reducing sugars resulting from the enzymatic action of diastase upon starch. In this 1.6 cc of venous blood is mixed with 10.4 cc of a 1 % sodium fluoride solution to prevent glycolysis and coagulation. 1.2 cc of this mixture, containing 0.96 cc of blood, is added to 1.8 cc of a phosphate buffer to obtain a pH of 6.8 for optimum activity of the diastatic enzyme. Then 5 cc of a 1 % starch solution in physiological saline is added and the mixture incubated at 37° C. The use of physiological saline insures equal concentrations of the chloride ion in the determination of diastatic activity. This procedure is carried out under strict aseptic conditions. After 3, 6 and 9 hours of incubation 0.1 cc of this solution was removed and tested for reducing sugars

by the method of HAGEDORN and JENSEN (9). Fasting blood sugar levels were taken before the experiment to determine the amount of sugar introduced with the blood. The difference between the initial sugar present and subsequent sugar determinations constitutes the amount of reducing sugars produced by the diastatic activity upon the starch substrate.

Results and Discussion

Using this method, the level of diastatic activity of the blood was determined in a group of ten normal healthy children, 3 to 12 years of age. Under physiological conditions it was found that the level of diastatic activity was remarkably constant for a single individual and the values for different individuals fluctuate within very narrow limits. In this series of ten children, the average value was 1.13 after three hours of incubation, 1.64 after six hours and 1.90 after nine hours of incubation. (Table 1.) To determine the variation of diastatic activity of the blood under conditions of hypochloremia, normal children were maintained upon a low chloride diet until the level of chloride excretion in the urine dropped below 0.2 %. According to MEYER and BISCH (10), this is the minimum level of urinary chloride obtainable and indicates the greatest possible fall of blood chloride levels, which can be reached without the appearance of dangerous symptoms. A strict diet must be maintained for two or three weeks to achieve this.

Table I

Values of Blood Diastatic Activity under
Physiological Conditions.

Child age in years	P.H. 13	P.A. 10	E.B. 10	N.A. 6	K.D. 6	T.S. 5	A.K. 5	R.K. 5	R.A. 4	M.D. 3	Average values
<i>Incubation</i>											
3 Hours	1.10	1.04	1.41	0.97	1.15	1.08	1.15	1.15	1.06	1.20	1.13
6 "	1.68	1.77	1.73	1.40	1.66	1.61	1.72	1.61	1.59	1.66	1.64
9 "	2.00	2.00	1.95	1.68	1.93	1.86	2.00	1.79	1.86	1.88	1.90

Table II

Values of Blood Diastatic Activity under Hypochloremic Conditions.

Child	P.H.	P.A.	E.B.	N.A.	K.D.	T.S.	A.K.	R.K.	R.A.	M.D.	Average values
<i>Incubation</i>											
3 Hours	1.13	1.10	1.06	0.95	1.01	0.79	1.02	1.02	0.88	0.99	0.97
6 "	1.59	1.55	1.48	1.29	1.43	1.39	1.46	1.50	1.43	1.35	1.44
9 "	1.70	1.66	1.66	1.48	1.63	1.68	1.68	1.70	1.61	1.57	1.63

When the blood diastase levels were taken under this condition of hypochloremia, the average results obtained after 3 hours were 0.97, 1.44 after six hours, and 1.63 after nine hours of incubation (Table II). These results indicate a significant fall in the levels of diastatic activity of the blood.

Table III

Diastatic Activity Following NaCl Injection in Hypochloremic Children.

Child	P.H.	P.A.	E.B.	N.A.	K.D.	T.S.	A.K.	R.K.	R.A.	M.D.	Average values
<i>Incubation</i>											
<i>30 Minutes after Injection.</i>											
3 Hours	1.15	0.99	1.20	0.99	1.13	0.92	1.13	1.04	1.02	1.13	1.07
6 "	1.70	1.46	1.46	1.32	1.50	1.52	1.72	1.59	1.50	1.50	1.56
9 "	1.82	1.68	1.70	1.54	1.84	1.73	1.97	1.77	1.70	1.77	1.71
<i>60 Minutes after Injection.</i>											
3 "	1.22	1.04	1.25	1.04	1.17	1.15	1.20	1.17	1.13	1.22	1.16
6 "	1.91	1.68	1.55	1.36	1.63	1.59	1.79	1.63	1.59	1.50	1.62
9 "	2.13	1.80	1.75	1.63	1.88	1.79	2.00	1.81	1.70	1.82	1.83
<i>120 Minutes after Injection.</i>											
3 "	1.17	1.01	1.20	1.01	1.08	0.97	1.15	1.15	1.10	1.17	1.10
6 "	1.86	1.66	1.43	1.32	1.57	1.57	1.73	1.55	1.55	1.50	1.57
9 "	1.04	1.80	1.68	1.64	1.81	1.73	1.90	1.81	1.66	1.75	1.78

Table IV

Blood Diastase Levels after 9 Hours Incubation in
Pathological Conditions.

Name	Age in years	Diagnosis	Value of blood plastase
DK	5	Septicemia	1.46
MA	4	Atrophy	1.25
HK	4	Bronchopneumonia	.77
AK	4	"	1.29
MP	12	"	1.08
AE	2	"	1.29
SH	2	Tuberculosis	1.45
BI	5	Enterocolitis	1.52
MI	3	Septicemia	1.10
SP	10	Pyelonephritis	.77
AI	3	Purpura	1.25
KA	8	Leukemia	.83
PP	4	Kala-Azar	2.28
MK	5	"	2.32
TK	5	"	2.38
HM	4	Malaria	2.24
AA	5	"	2.38
TK	5	Cooley's Anemia	2.11
MG	5	" "	1.97

To further demonstrate the relationship of the diastatic activity to the level of blood chloride, 80 to 100 cc of physiological saline was administrated intravenously to these hypochloremic children, and blood samples were removed 30, 60 and 120 minutes following injection to observe changes in activity.

The results of this experiment (Table III), show a significant rise in the blood levels of diastatic activity which becomes apparent after 30 minutes, reaches a maximum, approaching normal values, after one hour and is still maintained when observed one hour later.

The third phase of this study was to investigate the levels of the diastatic activity of the blood in pathological conditions where there is a severe reduction of chlorides in the urine as a result of

hypochloremia. In severe infectious diseases such as pneumonia, tuberculosis, typhoid, dysentery and acute gastroenteritis cases in children, previous investigators have recognized the existence of hypochloremic conditions. KELLER (11) has attempted to explain this effect as a biochemical phenomenon in which sodium tends to be retained in the interstitial fluid while there is an increased excretion of chloride and potassium in the urine. In our studies of several cases of severe infectious diseases, atrophy and toxicosis, there has been found a marked decrease in the level of diastatic activity of the blood (Table IV). Similar results have been observed by LOESCHKE (2).

We have also studied the level of diastatic activity in several cases of parasitic diseases, malaria, kala-azar, and two cases of COOLEY's anemia. In these cases, there was a significant increase in the level of blood diastase. It is not possible, at this time to correlate the blood chloride levels do diastatic activity in COOLEY's anemia and kala-azar, as investigation upon chloride retention in these diseases is still being studied at our Clinic. However, MOROVITZ and WONNENBRUCH (12) have consistently observed chloride retention in the blood in cases of malaria.

I wish to express my deep gratitude to Dr. J. M. ORTEN, Professor of Biochemistry at Wayne University and to Dr. R. STEWART for their valuable suggestions in writing the article.

Conclusions

The following conclusions can be drawn from the results of the preceding experiments.

1. The level of diastatic activity in the blood of children, determined by the method described by CHROMETZKA and ERLEMANN, shows little fluctuation from a mean value of 1.90 after nine hours of incubation.
2. After a prolonged low chloride diet, the level of diastase found in blood is reduced.
3. Intravenous injection of 0.9 % saline to experimental hypochloremic children, restores the level of diastase in the blood.
4. In severe diseases, the reduction of blood diastase which has previously been attributed to a decrease of secretion of diastase of the exocrine glands, may be due in part to an impairment of diastase activity in the other tissues of the body in which diastase is found. This may be

related to the decreased blood chlorides, which have been found in these conditions.

5. There has been observed a definite increase in blood diastase in the parasitic diseases of malaria, kala-azar and in COOLEY's anemia.

JOHN B. NICOPoulos: *Études sur l'activité diastasique du sang chez les enfants.*

Les conclusions suivantes peuvent être tirées des résultats des expériences précédentes:

1. Le niveau de l'activité diastasique dans le sang déterminé au moyen de la méthode décrite par CHROMETZKA et ERLEMANN, montre une petite fluctuation à partir de la valeur moyenne de 1.90 après 9 heures d'incubation.

2. Après un régime prolongé faible en chlorures, le niveau de diastase trouvé dans le sang est réduit.

3. Une injection intraveineuse de sérum salé à 0.9 %, chez les enfants soumis à une hypochlorémie expérimentale, restaure le niveau de diastase observable dans le sang.

4. Dans les maladies sévères, la réduction de la diastase sanguine qui avait été attribuée auparavant à une diminution de sécrétion de diastase par les glandes exocrines, peut être due en partie à l'affaiblissement de l'activité diastasique dans les autres tissus du corps où l'on trouve des diastases. Cela peut être réalisé par la diminution des chlorures du sang qui a été trouvée dans ces conditions.

5. On a observé une diminution définie de la diastase sanguine dans la maladie de COOLEY.

JOHN B. NICOPoulos: *Untersuchungen über die Diastasewirkung im Blut von Kindern.*

Aus den obigen Versuchen können folgende Schlussfolgerungen gezogen werden.

1. Der Grad der Diastasewirkung im Blut von Kindern, nach den Methoden von CHROMETZKA und ERLEMANN bestimmt, zeigt geringe Abweichungen vom Durchschnittswerte 1.90 nach 9-stündiger Brutzeit.

1. Nach einer längeren chloridarmen Kost findet man einen reduzierten Diastasewert im Blut.

3. Bei experimentell hypochlorämisch gemachten Kindern führt die intravenöse Injektion von 0.9 %iger Kochsalzlösung zur Wiederherstellung des im Blute nachweisbaren Diastasespiegels.

4. Bei schweren Erkrankungen dürfte die Verminderung der Blutdiastase, die früher einer herabgesetzten Diastasesekretion der exokrinen Drüsen zugeschrieben wurde, teilweise eine Folge der Schädigung der Diastasebildung in anderen Körpergeweben sein, wo Diastase nachge-

wiesen wird. Dies dürfte auf den verminderten Chloridwerten im Blut beruhen, welche man bei solchen Zuständen fand.

5. Bei parasitären Krankheiten wie Malaria, Kala-azar und bei COOLEY-Anämie fand man deutliche Erhöhungen der Diastasewerte im Blut.

JOHN B. NICOPOULOS: *Estudios sobre la actividad diastásica de la sangre en los niños.*

De las experiencias realizadas pueden sacarse las siguientes conclusiones:

1. El nivel de la actividad diastásica en la sangre determinado por medio del método descrito por CHROMETZKA y ERLEMANN muestra una pequeña fluctuación a partir de los valores medios de 1.90 tras 9 horas de incubación.

2. Después de un régimen prolongado pobre en cloruros la tasa sanguínea de diastasa es reducida.

3. Una inyección intravenosa de suero salino al 0.9 % en niños sometidos a una hipocloremia experimental restaura los valores de diastasa en la sangre.

4. En las enfermedades severas, la reducción de las cifras de diastasa en sangre que en otro tiempo se había atribuido a la disminución de secreción de diastasa por las glándulas endocrinas, puede ser debido en parte a un debilitamiento de la actividad diastásica en los otros tejidos del organismo, en los cuales se encuentran diastasas. Ello puede realizarse por la disminución de los cloruros sanguíneos que se ha encontrado en estos casos.

5. Se ha encontrado una disminución manifiesta de la diastasa sanguínea en enfermedades parasitarias como el paludismo y Kala-Azar y en la anemia de COOLEY.

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FROM THE PEDIATRIC CLINIC OF THE AKADEMISKA SJUKHUSET,
UPPSALA (CHIEF: PROFESSOR B. VAHLQUIST) AND THE PEDIATRIC
CLINIC OF KAROLINSKA INSTITUTET, NORRTULL'S HOSPITAL, STOCKHOLM
(CHIEF: PROFESSOR A. WALLGREN).

Experimental Inoculation of Roseola Infantum

by

BO HELLSTRÖM and BO VAHLQUIST

Roseola infantum (exanthema subitum) is a clearly definable acute exanthematous disease. Its clinical appearance has been well and thoroughly described (BREESE, 1941, CLEMENS, 1945, BERENBERG, WRIGHT and JANEWAY, 1949) and it can now be said to have been established as a disease *sui generis*. It is not an atypical form of influenza, nor is it an allergic manifestation occurring in various acute infectious diseases, as has been suggested previously. Like measles and German measles, it is, definitely, a children's disease. Experience indicates that, in frequency, it does not come far behind these two diseases with which it has, in fact, much in common. On the other hand, as far as measles and German measles are concerned, there is definite epidemiological and experimental evidence of a virus etiology whereas, in the case of roseola infantum, the epidemiological observations have been contradictory and experimental investigations have so far failed to substantiate a virus etiology.

Certain seasonal variations have been noted. CLEMENS described 80 cases, 48 of which (55 per cent) occurred in February, March and April and 13 (16 per cent) in October, a seasonal variation that was similar to what is found in measles, German measles and scarlet fever.

The age of predilection is from $\frac{1}{2}$ to 3 years (BERENBERG et al.). The passive immunity imparted by the mother may protect the child during the first months of life, and thereafter the infection is

so widely spread that, by the age of 3 years, most children will have acquired an active immunity. As to its infectiousness data differ. Several authors, (WESTCOTT, 1921, and ROSENBUSCH, 1939, among others) state that secondary cases are rare, possibly owing to the shortness of the age of predilection. However small epidemics at public nurseries have been described (CUSHING, 1927). JAMES and FREIER, 1949, gave an account of an epidemic, at a maternity hospital, the course of which is worthy of note, especially with regard to the age of those infected. 19 of 65 infants were attacked at an average age of only 11 days and, in addition, a number of adults, including parents and nurses.

The incubation period is fixed at about 10 days by most authors (CUSHING, 1927, BREESE, 1941).

Two earlier reports deal with attempts to ascertain the presence of an infectious agent, if any, and, more particularly, to trace a filtrable virus, as it has never proved possible by bacteriologic methods to isolate a pathogen. BREESE swabbed the throat of three infants in the pre-eruptive stage of the disease with cotton saturated with meat extract broth. The material was then filtered through small Seitz filters. The filtrate was applied to the scarified cornea of rabbits and injected intracerebrally and intraperitoneally into different test animals. In addition, blood was taken from a patient in the pre-eruptive stage of the disease, the serum being transferred to the chorio-allantoic membrane of a chick embryo. One of the throat samples was also inoculated into such a membrane. All these attempts at isolating a filtrable virus failed. BERENBERG et al. collected nasopharyngeal washings and cerebrospinal fluid from 6 patients also in the febrile pre-eruptive stage and inoculated mice intranasally, intracerebrally and intraperitoneally. In 2 cases chick-embryos were inoculated. In none of these instances could any virus be isolated.

Some of these related experiments may have failed due to a lack of pathogenicity for the test animals. In such an event, the prospects of success should be better in inoculation tests on human volunteers. Such tests have been performed with the virus of German measles by HIRO and TASAKA (1938), and

the virus of measles by SHAFFER et al. (1941), and others. Both these diseases have also been communicated to monkeys (SHAFFER et al., HABEL, 1942). No definite data are available of any positive results following experimental inoculation of these viruses into animals other than monkeys.

Present investigation: As roseola infantum is an extremely benign disease, practically without any known complications or after-effects, and as spontaneous infections occur in, perhaps, most children, inoculation experiments on man have been regarded by the authors as permissible. Every case so inoculated was either a severely deformed or mentally deficient child with a definitely bad prognosis of life or mental development.

The material consists of 14 inoculation tests, from 12 definite cases of roseola infantum. From these 12 cases 2—5 ml of heparinized venous blood was taken, usually on the first day of the exanthem. Donors and subjects have been placed in different departments, without any possibility of contact. The blood was given intramuscularly without centrifugation or filtration. Those inoculated have then been examined daily with regard to temperature, catarrhal symptoms, the appearance of adenitis and exanthem. Further, up to at least a fortnight after the inoculation, frequent examinations of the blood have been performed with determination of the total number of leukocytes and differential counts. The inoculated cases include infants aged from 2 to 17 months.

Three of the 14 inoculation tests produced unquestionably positive results. In another two cases the inoculation tests probably succeeded, but since they appeared to be atypical in some respect, they have been eliminated. The other cases have not reacted. A detailed account of the 3 definite cases will be given below. The results are also given in diagrams (Figs. 1—3), and in Table 1. where the changes in the blood are set forth in more detail.

Case 1. F 145/48, Norrtull's Hospital. A girl, 5 months old with a diagnosis of myelomeningocele and hydrocephalus. On the fourth day of the disease, 5 ml heparinized blood was taken from a typical case of roseola infantum and injected intramuscularly. (Fig. 1, Table 1). On the sixth day after inoculation and on the next following days, the tempera-

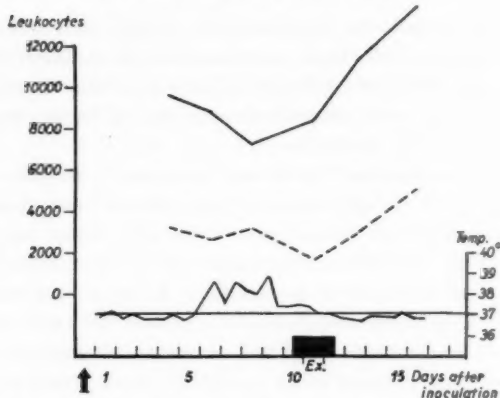


Fig. 1. Temperature, leukocytes and time of appearance of exanthema. Continuous line: Total number of leukocytes, Dotted line: Number of neutrophils. Case 1.

ture of the inoculated child rose up to between 38 and 39° C. In the afternoon of the ninth day the temperature fell. On the tenth day, maculae of a pale red, the size of 2—5 mm appeared on the body. Simultaneously a neutropenia occurred. No catarrhal or neurological symptoms occurred nor any swelling of lymphatic glands.

Case 2. F 121/50, Norrtull's Hospital. Girl aged 5 $\frac{1}{2}$ months. Diagnosis: encephalopathy and microcephaly (Fig. 2, Table 1). 5 ml heparinized blood was transferred from a definite case of roseola infantum on the fourth day of the disease. On the seventh day after inoculation, she developed a temperature which, during the following days, kept about 38 and 39.2° C. On the eleventh day, the temperature fell. On the night before, an exanthem had appeared, reaching its maximum, in intensity and extension, on the eleventh day. It remained unchanged on the twelfth day, paling and disappearing during the night before the thirteenth day. The exanthem was fine and macular and moderately red with a slight cyanotic colouring. It began on the body, spreading peripherally to the extremities and the head. Simultaneously with the exanthem, a marked decrease of the polynuclear cellular elements occurred with a leukopenia of 4 600 cells and a relative lymphocytosis (65 per cent). During the pyrexial state the pharynx reddened a little, while the cervical glands became slightly swollen. No neurologic symptoms occurred. There was no deterioration in the previously bad general condition.

Case 3. 692/43. The Akademiska Sjukhuset, Uppsala. Children's Department. A boy, aged 3 $\frac{1}{2}$ months. Diagnosis: mongolism. On the

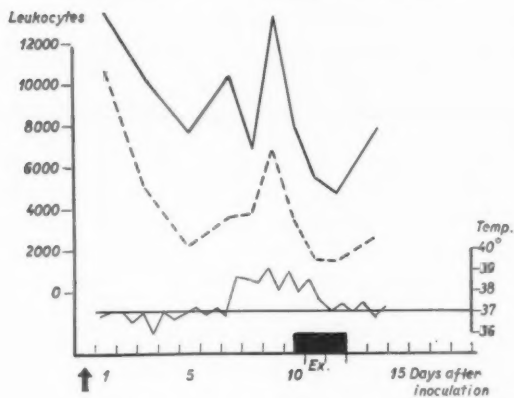


Fig. 2. Case 2. (As in fig. 1.)

fifth day, 2.5 ml of heparinized blood from a definite case of roseola infantum were drawn and injected (Fig. 3, Table 1). Nine days after inoculation the inoculated child showed a rise in temperature. On the tenth and eleventh days it was 38° C. On the twelfth day, the temperature fell to normal. Simultaneously, the exanthem began and on the following day spread from the trunk to other parts. On the fourteenth day the exanthem paled. The neutropenia was not marked in this case. No catarrhal or neurologic symptoms occurred.

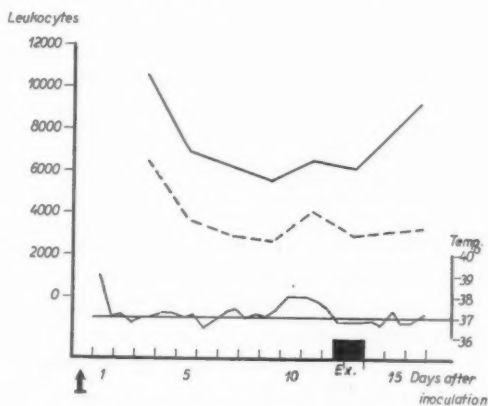


Fig. 3. Case 3. (As in fig. 1.)

Table 1.

Blood changes (the white cell picture) in the three positive transfer tests.

	Days after inoculation	Total leukocyte count	Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes	Plasma cells
Case 1.	4	9,600	2,880	380	—	5,570	770	—
	6	8,800	2,200	440	—	5,630	530	—
	8	7,200	3,170	—	—	3,460	570	—
	11	8,400	1,600	80	—	6,380	340	—
	13	11,200	2,910	—	—	7,620	670	—
	16	14,400	4,900	—	—	9,070	430	—
Case 2.	1	14,000	10,360	560	—	2,800	280	—
	3	10,200	5,100	—	—	4,900	200	—
	5	7,600	1,980	150	—	5,470	—	—
	7	10,400	4,580	—	—	4,160	1,660	—
	8	6,800	3,740	—	—	1,970	1,090	—
	9	13,200	7,130	—	—	4,090	1,980	—
	10	7,800	2,960	—	—	3,670	1,170	—
	11	5,400	1,510	—	—	3,510	380	—
	12	4,600	1,430	—	—	2,670	500	—
	14	7,800	2,650	—	—	4,370	780	—
Case 3.	3	10,500	6,510	100	—	2,630	1,260	—
	5	6,900	3,310	200	140	2,690	560	—
	7	6,100	2,870	180	60	1,950	980	60
	9	5,500	2,700	170	50	1,380	1,150	50
	11	6,500	4,030	—	—	1,820	590	60
	13	6,100	2,990	60	—	2,620	240	190
	16	9,100	3,190	—	—	4,910	910	90

The three definitely positive inoculation tests appear to show that in roseola infantum an infectious agent is circulating in the blood. It has not been possible by bacteriologic methods to isolate a pathogen, a fact that suggests a virus as the infectious agent. The incubation period was, in our cases, 6—9 days before the onset of the pyrexia, i. e., a little less than is usual in roseola infantum (10 days). This indicates that the infectious

agent causes a more rapid onset of the disease when experimentally inoculated intramuscularly than by the "natural" way of infection, i. e., probably the air passages.

The failure of most of our inoculation experiments may depend on many factors. As already stated, the blood was taken from the donors during the afebrile stage of the exanthem, when the infectious agent may, perhaps, have vanished from the blood. It is, further, possible that this agent is susceptible to external mechanical or thermal factors connected with the inoculation. In some of the failures, a passive immunity transferred from the mother may play a part. However, the age distribution of the positive cases, compared with the negative ones, hardly provides any support for such a contention. In the "atypical cases" a passive immunity may have played a rôle in modifying the course. The predominating number of negative cases is, at any rate, of subordinate significance with regard to the particular purpose of the investigation, since the essential point is that the presence in the blood of an infectious agent has, in some cases, been established and that, when transferred from one person to another, by intramuscular injection, it has produced an identical typical disease picture.

Summary

In 14 cases, attempts were made to transfer the infecting agent of roseola infantum through intramuscular injection of blood from typical cases in the exanthematous stage.

Three of these cases revealed a typical symptom complex with pyrexia beginning on the 6th—9th day, followed by a fall in the temperature on the 9th—12th day with a simultaneous exanthem. Blood changes occurred with neutropenia and relative lymphocytosis.

The results suggest that an infectious agent circulates in the blood in roseola infantum.

B. HELLSTRÖM et B. VAHLQUIST: *L'inoculation expérimentale de roseola infantum.*

On a essayé dans 14 cas de transférer roseola infantum par injection intramusculaire du sang provenant des cas typiques de l'étage exanthema-

teux. Trois de ces cas montraient la symptomatologie typique avec pyrexie commençant le 6^{ième}—9^{ième} jour, suivi par une chute de température pendant le 9^{ième}—12^{ième} jour avec un exanthème simultané. L'aspect du sang changeait avec "neutropenia" et "lymphocytosis" relatives.

Dans le cas de la roseole infantile, les résultats supposent qu'un contagion circule dans le sang.

B. HELLSTRÖM und B. VAHLQUIST: *Über die experimentelle Inokulation von Roseola infantum.*

Man machte in 14 Fällen den Versuch, Roseola infantum durch intramuskuläre Injektion von Blut von typischen, im Exanthemstadium befindlichen Fällen zu übertragen.

3 dieser Fälle entwickelten einen typischen Symptomkomplex mit am 6.—9. Tage einsetzendem Fieber, dem am 9.—12. Tage ein Temperatursturz bei gleichzeitigem Exanthemausbruch folgte. Die Blutveränderungen äusserten sich in Neutropenie und relativer Lymphozytose.

Die Ergebnisse lassen bei Roseola infantum einen im Blute kreisenden Erreger vermuten.

B. HELLSTRÖM y B. VAHLQUIST: *Inoculación experimental del roséola infantum.*

En 14 casos se ha intentado transmitir la roséola infantum, por inyección intramuscular de sangre extraída de casos típicos en la fase exantemática.

3 de estos casos revelaron un complejo típico de síntomas de pirexia que se inició entre el sexto y noveno día, con descenso de la temperatura entre el noveno y duodécimo día y aparición simultánea del exantema. Los cambios de sangre aparecían con neutropenia y linfocitosis relativa.

El resultado sugiere que el agente de la enfermedad en la roséola infantum se propaga en la sangre.

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Addendum

After the conclusion of the present investigation a report has been published by KEMPE, SHAW, JACKSON, and SILVER in the *Journal of Pediatrics* (October, 1950) of a positive transfer experiment in one case in man.

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Potassium Studies in Pediatric Diseases (pyloric stenosis, renal failure, and diabetic acidosis)¹

by

**T. S. DANOWSKI, L. GREENMAN, J. H. PETERS, F. A. WEIGAND,
H. A. MERMELSTEIN, W. B. PARSONS and F. M. MATEER**

The attention of the clinical investigator and the concern of the pediatrician have increasingly turned to changes in cell constituents occurring in illness and disease. This in no wise means of course that all questions relevant to the other major component of body fluid, i. e. the extracellular water and solutes, have been resolved. It does indicate however that currently all of the water and electrolyte subdivisions of the body, outside and inside of cells, are being critically evaluated in bedside situations. In many ways this is not a simple task, since at present it is usually possible only to define changes in cells by indirect evidence rather than direct analysis. This involves not only the measurement of various serum components, but necessitates also a careful accounting of all intake and output. Studies along these lines are yielding clinically applicable information. Our interests have centered about the electrolyte, nitrogen, carbohydrate and water changes in vomiting infants, in children with far advanced renal insufficiency and in juvenile diabetics undergoing treatment for acidosis or coma.²

A. Potassium changes during recovery from vomiting. Pyloric stenosis with attendant vomiting, dehydration and starvation has

¹ Presented before the American Academy of Pediatrics at San Francisco.

² Case 1 has been presented elsewhere. The remainder represent unpublished material.

of course long been recognized as productive of hypochloremia, increased plasma carbon dioxide content and azotemia (15, 16, 19, 23, 24). During the past year a series of such infants, 13 in number, has been studied by the balance method (4, 5). In no instance has it been possible, for obvious reasons, to follow these subjects from the inception of the illness. Furthermore, vomiting ceased following entry into the hospital and withdrawal of oral intake. Hence the data available really represent: a) status on admission, b) changes in the course of parenteral therapy and surgery, RAMSTEDT procedure, and c) observations during oral intake. A representative case, T. B., is depicted in Figure 1.

On admission this 3 $\frac{1}{2}$ week old male infant was found to have a sodium level of 139 milliequivalents per liter, serum chloride concentration lowered to 78.0 milliequivalents per liter, and the serum content of carbon dioxide raised to 37.3 milliequivalents per liter. In addition the blood NPN was elevated to 44 milligrams percent and, though not evident in the figure, plasma dehydration was present. The concentration of serum potassium at the start of the study was 4.3 milliequivalents per liter. Nonetheless it is reasonable to suggest that this patient had a deficit of body potassium. First, studies of others as well as our own indicate that vomitus contains considerable amounts of potassium in levels in excess of those in extracellular fluid (1, 17, 22). This infant had vomited for days preceding admission; the patient was also starved and dehydrated. Such changes produce marked deficits of cell potassium (10, 12, 30). It is evident from Figure 1 that this infant was still losing potassium in urine following admission. This by itself accounts for the recorded negative potassium balances, since there were no losses in stool or vomitus. The normal serum potassium concentration in this patient is not surprising, since it is obvious that levels of serum potassium are the resultant of various processes. Thus, if starvation and dehydration are minimal while losses in vomitus and urine are extensive the potassium level will in all probability be low. Such a trend would be accentuated by potassium transfers into cells or by the expansion of body water with fluids low in potassium (3, 4). If on the other hand potassium leaves cells and is not lost from the

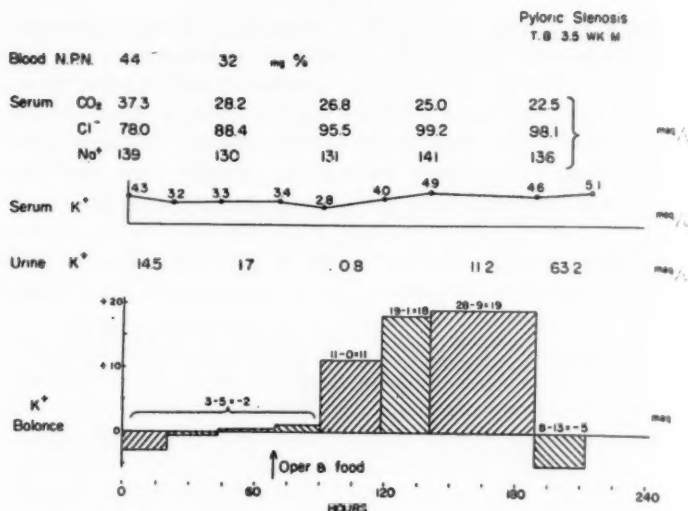


Figure 1. Electrolyte changes in pyloric stenosis.

Potassium data and serum electrolyte changes presented above are discussed in the text. The following additional information is available: on the basis of 24 hour periods per kg body weight, this 2.78 kg infant preoperatively retained 4.8 meq Na and 6.8 meq Cl. Postoperatively on a milk formula he developed positive balances of Na, 3 meq; Cl, 5.4 meq; and of N, 0.41 gram per kg per day.

body, values in serum rise. Such elevations are augmented by losses of body water without potassium, as in insensible perspiration. Finally it is not unreasonable to find, as in patient T.B., that these changes may cancel one another, resulting in a normal serum potassium level on admission. Following potassium-free fluids hypokassemia developed in this patient. This was either a dilution, an internal transfer phenomenon, or both, since the infant was no longer vomiting and urinary losses became negligible. Difficulties in estimating changes in the extracellular space prevent quantitation of these two processes (4). Following the resumption of an intake of foods which contained potassium, the balance of this electrolyte became positive and serum and urine concentrations rose (Figure 1); 88 percent of the potassium retained

entered the cells. The serum carbon dioxide content fell to 22.5 and the chloride finally rose to 98.1 milliequivalents per liter. In the last period there is evidence that deficits of body potassium had been cancelled, since urine potassium concentrations rose to 63.2 milliequivalents per liter, the highest recorded in this patient, and a negative external balance of this electrolyte appeared. From the antecedent balance data it seems reasonable to deduce that the infant had developed during his illness a negative balance of potassium of about 43 milliequivalents. This equalled 14.3 milliequivalents per kilogram of body weight and approximated one-fifth of his estimated total body potassium.

Another instance of pyloric stenosis in a 5 week old male infant, J. S., indicated that treatment with intravenous potassium salts prevents hypokaliemia and obviated low U/P ratios of potassium (5, 26). This patient had hypochloremia, 83.8 milliequivalents per liter, and an elevated serum CO_2 content of 31.2 milliequivalents per liter. Serum sodium was normal. Prior to potassium therapy serum levels of potassium had fallen to 3.7 (Figure 2). Of the 35 milliequivalents of this cation which were administered intravenously in the first $1\frac{1}{2}$ days 33 were retained. All but one-tenth of this amount represented entry into cells. During the post-operative period the balance remained positive; the patient retained a total of 40 milliequivalents of potassium, averaging 8.2 per kilogram of body weight with 90 percent of this passing into the cells. The balance data in Figure 2 indicate that at the end of this interval potassium deficits had been cancelled and that the patient had retained considerable amounts of sodium, chloride, water, and nitrogen as well.

B. *Metabolism of potassium in far advanced renal insufficiency.* Renal disease usually modifies the disposition of potassium which enters the extracellular pool in intake or from body cells. Since urinary excretion is the chief route for disposal of potassium excesses, it is obvious that with inadequate renal function hyperkalemia may appear (11, 20, 21, 25). This sequence was noted in an 11 year old girl, J. B., with acute glomerulonephritis. Following progressive oliguria and anuria the serum potassium was 9.7

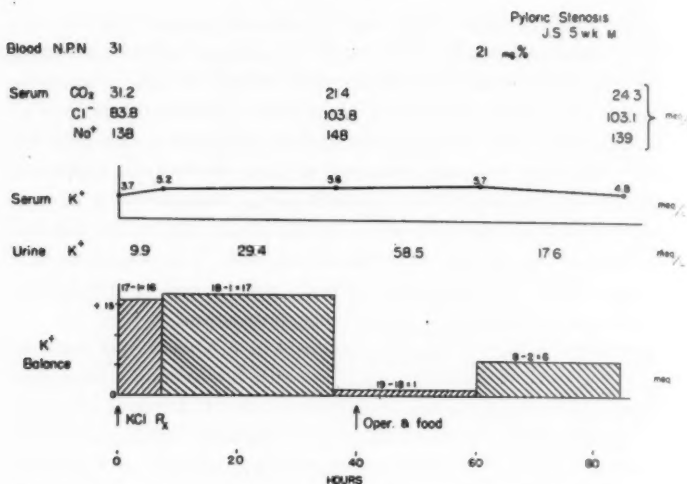


Figure 2. Potassium repletion during recovery from vomiting.

In addition to the data presented in the figure this infant, weighing 3.82 kg, preoperatively retained 5.9 meq Na and 11.8 meq Cl, while losing 0.03 gram N; all these values in terms of per kg per 24 hours. Postoperatively, on a milk formula, body supplies of Na, Cl, and N increased by 2.9 meq, 4.5 meq, and 0.05 gram, respectively, per kg per day.

meq. per liter (Figure 3). At that time the blood NPN had reached 151 milligrams percent and the serum dioxide content had decreased to 16.2 milliequivalents per liter. The ECG showed peaking of the T wave, a change which frequently appears during hyperpotassemia. Subsequently the ECG showed the loss of P waves and the disruption of the QRS complex characteristic of potassium intoxication (11, 28, 31). The patient died despite partially successful attempts to lower the potassium level by gastric lavage, dilution with potassium-free fluids and the administration of insulin and glucose. A total of 14 milliequivalents of potassium were removed by these means without a significant transfer of the cation into cells. An additional 75 milliequivalents were lost in a diarrheal stool.

It must not be concluded however from this example that potassium intoxication is an invariable concomitant of renal

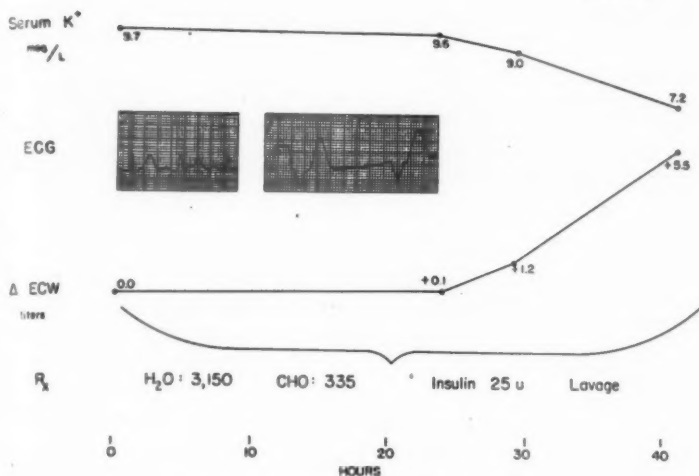
ANURIA
J.B. 11 F

Figure 3. Potassium intoxication in anuria.

Additional balance data on this patient showed a total Na retention of 384 meq and a Cl gain of 238 meq in the extracellular fluid, coinciding with the increase in edema. Serum concentrations of Na varied between 121 and 118 meq/l, CO₂ dropped from 16.2 to 12.6 meq/l, and Cl decreased further from 89.0 to 74.6 meq/l. The lower figures in each instance represent values shortly before death.

failure. In the majority of patients urinary excretion of this electrolyte is well maintained and extracellular accumulation does not appear (11). As a matter of fact, at times hypokassemia may develop (Figure 4). This 12 year old girl, A. E., was found to have a serum potassium level of 2.3 milliequivalents per liter. The blood NPN was 92 milligrams percent. The low serum water, 916 grams per liter, indicated that the hypokalemia could not be explained by dilution. It seems far more reasonable to attribute the observed decrease in potassium to earlier losses in vomitus or in urine. The patient was subsequently given KCl intravenously. Serum levels of this cation rose to normal and ultimately supranormal ranges. There were however no beneficial effects. During the 4 days of extra potassium intake, 85 percent of the

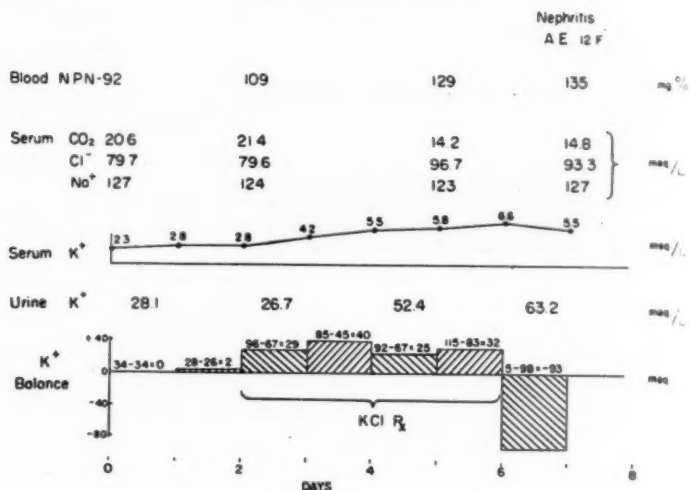


Figure 4. Potassium therapy in renal failure.

The NPN and K changes in this 20.5 kg girl with chronic pyelonephritis are discussed in the text. External balances of Na and Cl in meq per 24 hours per kg are summarized below:

\bar{a} K	during K	\bar{p} K
Na -0.3	-0.3	-1.1
Cl +0.2	+1.6	-3.0

In the periods before and after K administration 1.7 and 1.5 meq Na, respectively, entered the cells while 1.2 meq moved out of cells during K retention.

retained ion was transferred into cells. All of this was lost however in the final period. The NPN continued to rise while the serum CO₂ declined further. With the cessation of KCl injections most of the retained potassium was promptly excreted in the urine and the serum levels of potassium declined (Figure 4).

C. Potassium changes in diabetic acidosis or coma. Again, as in the case of the vomiting infants, it is impossible to present any data on the pretreatment phases of diabetic acidosis and coma. Nonetheless certain facts relevant to the metabolism of potassium during the prehospitalization and the treatment periods are well established. These are in great measure discernible in the graphic

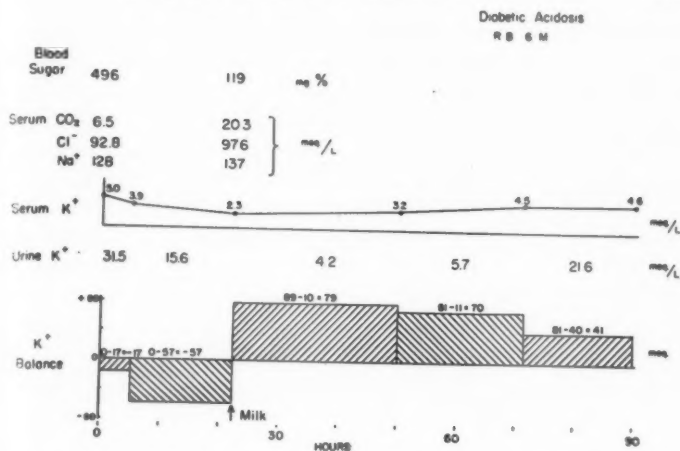


Figure 5. Electrolyte and nitrogen changes during therapy of diabetic coma.

In addition to the above, this 21 kg boy retained during the first 22 hours of therapy, on a per kg per day basis: 26.8 meq Na and 8.7 meq Cl, but lost 0.51 gram N. The cells gained 18.1 meq Na. During the next 3 days on milk formula the patient remained essentially in NaCl equilibrium.

presentation of the findings in a 6 year old boy, R. B., during therapy for diabetic coma. This patient was admitted overbreathing and semicomatose with a blood sugar of 496 milligrams percent, a serum CO_2 content of 6.5 milliequivalents per liter and a pH of 7.02 (Figure 5). Treatment, started immediately, consisted of crystalline insulin, and intravenous saline solution. At the end of 5 hours the patient had received 80 units of insulin with a fluid input of 1925 cc.; overbreathing disappeared, the blood sugar had dropped, and the serum CO_2 had risen slightly. At the end of the first day the levels of blood sugar and serum CO_2 and chloride were back to normal. The changes in the serum potassium during this and subsequent periods are of particular interest, since they are in the main representative of the findings in these subjects as a group (7, 18). In this patient the pretreatment concentration of this electrolyte in serum was 5.0 milliequivalents per liter (Figure 5). Following the administration of insulin and potassium-free fluids a distinct drop to 2.3 was ob-

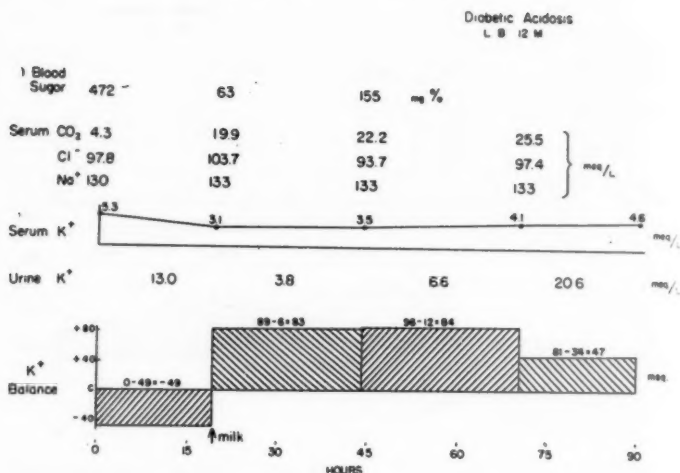


Figure 6. Potassium retention during recovery from diabetic coma.

During the first 19 hours this 32 kg child retained daily per kg of body weight: 6.3 meq Cl and 9.1 meq Na (one-third into cells), but lost 0.26 gram N. Essentially none of the Na gained was lost during the subsequent 3 days on milk.

served 23 hours after admission. At that time an *ad libitum* milk and water intake was instituted and the patient as a consequence received and retained significant amounts of potassium. More than 95 percent of this potassium entered cells. The serum potassium gradually returned to normal values as deficits of body potassium were cancelled inside and outside of cells.

It is not unexpected of course to find that patients in diabetic coma do develop deficits of body potassium. Cellular potassium moves into extracellular fluid as a result of dehydration, starvation, and the abolition of carbohydrate metabolism, changes which characteristically occur to a marked degree in diabetic acidosis and coma (2, 7, 18). This potassium can then be lost from the body in vomitus, in urine, or via other routes. Some of these processes are evident in the early hours of therapy in patient R. B., as well as in patient L. B., a 12 year old boy (Figure 6) in whom the symptoms, findings and the subsequent course of events

are comparable. Prior to the resumption of an oral intake both were in a negative potassium balance. In each the serum potassium levels declined as a result of urinary losses, transfers of potassium into cells, and dilution of the body fluids with potassium-free solution. As an accompaniment a marked decrease in urine potassium concentrations was observed. The institution of a milk diet and hence of an intake of potassium resulted in the retention of potassium and a gradual return of serum and urine concentrations to ordinary values. In both patients essentially all of the retained potassium entered the cells; however, a definite proportion of the positive intracellular balance reflected the deposition of nitrogen in cells (13). Similar positive balances have been observed by us in other juvenile diabetics, some 32 in number, during convalescence from acidosis or coma, irrespective of whether potassium was administered as a salt such as KCl or as a constituent of food (6, 7). Since potassium injected or ingested in excess of body needs is rapidly eliminated (29), it is reasonable to interpret the positive balances of potassium in this group of patients as indicative of previous depletion of this electrolyte.

Insofar as we have been able to determine from our own studies and those of others one of the chief differences between juvenile and adult diabetic subjects in acidosis or coma is the pretreatment potassium level (7, 18, 27). In the adult patient this is frequently above values seen in health, with or without underlying diabetes. This has not been true in most of the children whom we have studied. In our group the admission values for serum potassium were often within normal limits. The difference between these findings and those in adults is in all probability related to the duration and intensity of the acidosis or coma. Most of our patients were admitted at an early stage of their diabetic decompensation. None of our cases developed anuria, certainly a far-advanced manifestation of the shock of diabetic coma. It is not surprising, therefore, in view of the demonstrated association between renal failure and hyperkalemia, to find that adult patients are more often admitted with increased levels of serum potassium. As a group, they enter the hospital much later in the course of their complications. Furthermore these children usually

continue to receive insulin even as acidosis develops. These factors probably explain the differences in serum potassium levels on admission in these two groups of patients.

Comment

The material which has been presented clearly indicates that alterations of potassium metabolism can occur in a wide variety of otherwise unrelated clinical situations. Evidence has been cited indicating that in the recovery phases following vomiting as well as during the treatment of diabetic acidosis and coma abnormally low levels of serum potassium usually appear. In renal failure on the other hand hyperkalemia is encountered far more often than hypokalemia. The availability of balance data in these diseases of which only selected cases have herein been presented permit some discussion of the mechanisms responsible for such changes in body potassium. It seems reasonable to suggest for example that in all of these patients dehydration must have been present. This stemmed in part from an inadequate intake of water and in part from losses of body fluids through the skin and lungs, as well as in urine and gastrointestinal secretions. Such decreases in extracellular water have been shown to induce a movement of potassium out of cells (30). Similarly it is not unlikely that illness interfered with an adequate intake of calories and protein in these patients. This was certainly true in the vomiting infants, in the diabetics in acidosis and, to a lesser extent, in the children with renal failure. In these circumstances the effects of starvation on the potassium stores in cells become evident. During periods of negative cell nitrogen balance potassium is lost by the cells (10). It is also possible that the subjects with diabetic acidosis may be subject to losses of cell potassium beyond those attributable to dehydration and starvation. These include the potassium released with deglycogenation of the liver, and, by analogy with the blood cells, with the interruption of the usual rate of carbohydrate metabolism (2, 14). These various processes all tend to produce the same end result, *i. e.*, a movement of potassium out of cells. It seems highly probable from clinical

and experimental observations that such cell potassium deficits jeopardize the survival of the patient (3, 8, 9). In view of this fact the recognition of such alterations in the body stores of potassium becomes highly important. It should be emphasized that the level of serum potassium may not be down, even though such cell deficits exist. Obviously if potassium which has left cells remains in the extracellular water, and the latter remains constant in volume, the serum potassium levels will rise above normal. If, on the other hand, potassium is removed by one or more of several excretory, secretory or reparative processes from the extracellular fluid or if the volume of the latter is expanded, then serum potassium levels may decline below normal. In either case, however, the status of the underlying defect in the electrolyte composition of cells will remain unrepaired. The chief additional differences will consist of a) the risk of potassium intoxication with cardiac standstill if extracellular potassium levels rise; and b) the possibility of muscular paralysis if hypopotassemia supervenes (3). The cases which have been cited illustrate that a flexible attitude must be maintained in evaluating the potassium metabolism in any particular disease entity or in any one patient. Though the changes which can occur may at times involve common mechanisms, their quantitative aspects and even their directions can differ.

Summary

Some of the results of potassium studies in infants with pyloric stenosis, in children with renal failure, and in juvenile diabetics treated for acidosis or coma have been presented by means of illustrative cases. Mechanisms involved in potassium transfers in these situations have been discussed.

T. S. DANOWSKI, L. GREENMAN, J. H. PETERS, F. A. WEIGAND, H. A. MERMELSTEIN, W. B. PARSONS et F. M. MATEER: *Études du potassium dans les maladies infantiles* (sténose du pylore, maladie rénale et acidose diabétique).

Quelques uns des résultats de l'étude du potassium chez les enfants atteints de sténose du pylore, chez les enfants atteints de faiblesse rénale

et chez les jeunes diabétiques traités pour acidose ou coma, ont été présentés au moyen de cas illustrants. Les mécanismes invoqués dans les transports du potassium dans ces différentes situations ont été discutés.

T. S. DANOWSKI, L. GREENMAN, J. H. PETERS, F. A. WEIGAND, H. A. MERMELSTEIN, W. B. PARSONS und F. M. MATEER: *Kaliumbestimmungen bei Kinderkrankheiten* (Pylorusstenose, Nierenerkrankungen und Diabetesazidose).

Anhand von anschaulichen Fällen wurden einige Ergebnisse von Kaliumbestimmungen bei Neugeborenen mit Pylorusstenose, Kindern mit Nierenerkrankungen und bei jugendlichen Diabetikern mit Azidose oder Coma mitgeteilt. Die an diese Situationen geknüpften Mechanismen der Kaliumspiegelverschiebungen werden erörtert.

T. S. DANOWSKI, L. GREENMAN, J. H. PETERS, F. A. WEIGAND, H. A. MERMELSTEIN, W. B. PARSONS y F. M. MATEER: *Estudios sobre las alteraciones del potasio en las enfermedades infantiles* (estenosis pilórica, afecciones renales y acidosis diabetica).

Se presentan a través de casos bien demostrativos, algunos de los resultados estudiando las variaciones del potasio en lactantes con estenosis pilórica, niños con afecciones renales y jóvenes diabeticos en estado de acidosis o coma. Se discuten los mecanismos causantes de las variaciones de la tasa de potasio en estas enfermedades.

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TRAVAIL EXÉCUTÉ DANS LA CLINIQUE INFANTILE DE L'INSTITUT CAROLIN À L'HÔPITAL NORRTULL DE STOCKHOLM (MÉDECIN-CHEF: PROFESSEUR A. WALLGREN) ET DANS LE LABORATOIRE DE L'HÔPITAL STOCKSUND (CHEF DE LABORATOIRE: DOCTEUR G. WIDSTRÖM).

Quelques expériences concernant l'immunité antituberculeuse, effectuées à l'aide de bacilles radio-actifs

par

L. STRÖM et G. WIDSTRÖM

En 1941, ELY avait déjà essayé d'ajouter des isotopes radio-actifs à des bacilles. Il avait cultivé différentes sortes de bacilles sur des milieux contenant du phosphore radio-actif: Ces bacilles étaient injectés dans les veines de rats qui étaient ensuite tués, puis la radioactivité des différents organes fut examinée. K. A. JENSEN fit des expériences analogues avec des bacilles tuberculeux également.

Pour déterminer le temps que les bacilles tuberculeux mettent pour atteindre les différents organes lors d'une infection expérimentale sur des cobayes, et aussi pour étudier le mode de passage de ces bacilles, nous avons fait les expériences suivantes à l'Hôpital de Norrtull à Stockholm:

Du phosphore radio-actif fut ajouté au milieu liquide de DUBOS et on y a cultivé différentes souches de bacilles de KOCH. Après dix jours environ, les bacilles ont été séparés du milieu par centrifugation et lavage minutieux. Ensuite, les bacilles radio-actifs ont été inoculés à des cobayes, qui furent tués à différents intervalles de temps après l'infection. On a déterminé pour les différents organes l'activité par g de tissu. Le résultat de ces expériences découle du tableau ci-joint.

Une observation importante résulte de ces expériences, à savoir que, sans conteste, l'activité la plus forte est trouvée dans

les glandes lymphatiques et dans la moëlle osseuse, indépendamment du temps écoulé après l'inoculation. Après 12 et 24 heures, nous avons trouvé plus d'activité dans les glandes lymphatiques que dans les poumons. Ensuite l'activité dans les glandes lymphatiques diminue, par rapport à celle que l'on trouve dans les autres organes, et il y a une certaine harmonisation dans la répartition de l'activité. Après 12 heures, probablement déjà après 4 heures, nous avons la même concentration d'activité dans le sang et dans les urines. Ces résultats concernant la répartition de l'activité ont été confirmés d'une autre manière par SOLTYS et JENNINGS.

Pour ces expériences on a injecté des bacilles marqués dans les veines de cobayes. Par ce moyen, on voulait arriver à ce que tous les tissus, la circulation sanguine comprise, soient en contact en même temps avec le même nombre important de bacilles. On voulait savoir si les animaux immunisés réagiraient d'une autre manière que les animaux non préparés, en ce qui concerne la répartition et l'excrétion d'éléments radio-actifs.

Quatre groupes de cobayes ont été examinés. Les cobayes du premier groupe avait été inoculés 8 semaines avant l'infection expérimentale au moyen de bacilles tuberculeux bovins virulents. On infecta le 2^{ème} groupe avec les mêmes bacilles, 2 semaines avant l'injection de bacilles BCG-marqués. Les animaux du 3^{ème} groupe ont été vaccinés 3 semaines avant l'infection expérimentale par 7 mg de vaccin BCG ordinaire. Tous ces animaux étaient donc plus ou moins immunisés. Le 4^{ème} groupe était composé de sujets témoins sains et non-préparés. La radio-activité des bacilles marqués était de 1,27 mill. d'impulsions par minutes.

Les animaux ont été tués après 12 et 24 heures. On trouve une différence, entre la répartition de l'activité chez ces animaux qui ont été inoculés par l'injection intraveineuse et celle que l'on observe chez les animaux qui ont été inoculés par la voie sous-cutanée. La plus grande quantité semble avoir été retenue par le foie et la rate et non par les glandes lymphatiques. Il peut sembler étonnant que les poumons, premier filtre traversé par les bacilles après l'injection dans le réseau sanguin, n'aient pas assimilé plus de radio-activité. Il semble que l'activité disparaisse beaucoup plus vite chez les animaux immunisés que chez

Cobayes injectés de vaccin Calmette radio-actif. Activité par
gramme de tissu.

Cobayes	Grange bacter	Nombre d'heures après l'inf. i. v.	Glandes lymph.	Rate	Pou- mon	Rein	Foie	Moelle osseuse	Sang	Urine
1	K3 8 sem.	12	690	4 045	2 360	1 120	2 130	3 260	530	960
2	" "	12	1 380	9 350	2 310	934	2 460	2 500	410	—
3	" "	24	1 200	5 040	1 640	910	2 520	2 960	314	2 140
4	" "	24	925	4 090	1 380	1 840	3 780	1 400	340	1 140
5	K3 2 sem.	12	930	2 780	1 890	1 520	4 170	1 000	370	860
6	" "	24	650	4 720	—	1 000	3 040	1 625	890	530
7	BCG 3 sem.	12	1 360	1 980	1 980	—	3 600	2 500	380	860
8	" "	12	—	4 200	2 830	510	2 450	1 960	410	—
9	" "	12	1 680	2 560	2 230	—	4 750	3 120	245	520
10	" "	12	1 860	2 000	—	960	4 160	2 980	360	585
11	" "	24	980	2 300	—	1 050	2 170	710	312	1 000
12	" "	24	—	3 100	890	1 200	2 260	970	360	—
13	" "	24	1 000	3 820	930	500	3 750	—	385	1 170
14	" "	24	1 120	1 500	610	370	4 970	1 050	410	1 190
15	Contrôle	12	1 545	6 660	930	1 175	1 990	6 260	550	375
16	"	12	1 328	5 350	2 220	865	3 820	3 760	460	420
17	"	24	12 700	1 390	2 500	1 465	3 720	3 460	350	—
18	"	24	14 200	3 520	874	804	2 780	4 000	340	400

les animaux de contrôle. Dans des expériences on a pu remarquer la même tendance à voir s'établir une excrétion plus abondante de phosphore radio-actif chez les animaux vaccinés. On peut donc résumer: On trouve chez les animaux vaccinés une concentration de bacilles radio-actifs beaucoup plus forte dans l'urine que dans le sang, tandis que chez les animaux de contrôle, on trouve vite la même concentration dans le sang et dans l'urine. Cette augmentation de l'élimination en une substance radio-active pourrait donc être interprétée comme un signe d'immunité, et pourrait même donner le degré d'importance de l'immunité.

Des recherches complémentaires actuelles confirment les observations faites jusqu'ici. De telles expériences ont été faites

également en ce qui concerne d'autres infections et on y a observé la même augmentation d'élimination de substance radio-active chez les animaux immunisés.

Résumé

On a étudié la mode de passage de bacilles tuberculeux radio-actifs dans les organismes des cobayes, et leur dissémination dans les différents organes, ainsi que la concentration de bacilles radio-actifs dans l'urine et dans le sang. On trouve chez les animaux immunisés une augmentation de l'élimination de la substance radio-active augmentation qui pourrait être interprétée comme un signe d'immunité, et pourrait même donner le degré d'importance de cette immunité.

L. STRÖM and G. WIDSTRÖM: *Experiments with radio-active tubercle bacilli, relative to immunity against tuberculosis.*

Studies of the passage of radio-active tubercle bacilli through guinea pigs and of the dissemination of these bacilli in the various organs, as well as of their concentrations in the urine and the blood, are reported.

Elimination of the marked substance is found to be increased in the immunized animals, which increase might be interpreted as an indication of immunity and might further indicate the degree of that immunity.

L. STRÖM und G. WIDSTRÖM: *Einige Versuche über Immunität gegen Tuberkulose, ausgeführt mit Hilfe radioaktiver Bazillen.*

Die Verfasser studierten die Art der Passage radioaktiver Tuberkelbazillen im Körper von Meerschweinchen, ihre Verbreitung in den verschiedenen Organen sowie die Konzentration radioaktiver Bazillen im Harn und im Blut. Sie fanden bei den immunisierten Tieren eine vermehrte Elimination von radioaktiver Substanz die als ein Zeichen von Immunität gedeutet werden, ja sogar den Grad dieser Immunität angeben könnte.

L. STRÖM y G. WIDSTRÖM: *Algunos experimentos hechos sobre la inmunidad antituberculosa usando los bacilos radio activos.*

Se ha estudiado la manera de migración de los bacilos de la tuberculosis radio activos en los cuerpos de cobayos, y su deseminación en los diferentes organos, y tambien la concentración de bacilos radio activos en la urina y la sangre. Se nota en los animales inmunisados una augmentación de la eliminación de phosphoros marcados, augmentación que quiza puede interpretarse como una sena de inmunidad y pueda dar el grado de inportancia de esta inmunidad.

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The Children's Hospital in Bergen

by

ALFRED SUNDAL

The magnificent Freedom Gift from the Swedish nation to the Norwegian to commemorate Norway's recovery of freedom in May 1945 included a perfectly modern children's hospital in Bergen. This special hospital — Barneklubben i Bergen — is the first pediatric hospital in Norway outside Oslo. It is erected in the centre of Western Norway, and this beautiful white hospital stands at the foot of the mountain Ulriken. Here in Bergen, the town between the seven mountains, the Swedish architects, Dr. Gustaf Birch-Lindgren and Mr. Hornyanszky have created a modern masterpiece whose purity of architecture blends harmoniously with the beautiful scenery about it.

The Children's Hospital is close to Haukeland Hospital which serves as a central hospital for Bergen. Indeed, the Children's Hospital is a part of Haukeland Hospital from which it is separated only by a main street. Yet the two are closely linked to each other by a 140 metre-long tunnel which is kept warm and which leads to the Radiological Department and the other special departments as well as to the laundry, main kitchen, the dining room for the nurses and staff and the other component parts of Haukeland Hospital. This underground passage, which runs under the street, is most useful here in Bergen because of its harsh and rainy climate.

The Children's Hospital is a special pediatric hospital serving not only the town of Bergen, with a population of about 115 000, but also the whole of Western Norway. It is estimated that the Children's Hospital will meet the requirements for a pediatric hospital service of a population of 300 000 to 400 000. In addition to being a special hospital it is also a University hospital attached



Fig. 1. The Children's Hospital (Barneklínikken) in Bergen seen from the south-west. In the front the lecture-room, further to the left the polyclinic on the ground floor, on the first floor doctors' offices, library etc. The main building in the four uppermost storeys, rooms for mothers and ward sisters to the left, to the right departments for sick children. The isolation department is seen to the extreme right. Below the tunnel.

to the new University of Bergen inaugurated in August, 1948. The architects have succeeded in taking into account the many functions required of a hospital of this kind: — to serve as a pediatric hospital, to provide education and training for medical students, to promote research, to serve as a polyclinic, as a control station etc. Now, after nearly a year's experience, we who work here are unanimous in finding that these various requirements are fully met, the whole hospital being linked together into a complete unit as a children's hospital on modern lines.

A two-storied building facing north and south has a frontage to the street. This wing, which includes the polyclinic, laboratories, offices, lecture hall etc., is attached to the main hospital building which, with its six storeys, faces east and west. The four uppermost storeys consist of hospital departments. This large hospital building is connected to the east with a one-storeyed wing, the Isolation Department, which, owing to the steep character of the



Fig. 2. From the vestibule.

ground, provides direct entry from outside and is attached to the third floor of the main hospital building.

Let us look more closely at architectural details. In the two-storeyed wing housing the policlinic and offices facing the street, we find two entrances on the ground floor. The main entrance admits one to an elegant reception hall or vestibule, and the other entrance to the policlinic. The reception hall is very beautifully decorated by a circular illumination and round pillars. A large wall of glass facing south gives a view of a beautiful garden with a fountain represented by a playful monkey who sits and spouts water out of his mouth; it is the work of the artist Moldeklev of Bergen who is also responsible for a very beautiful and symbolic ceramic group on the wall at the end of the hall. This diagonal design represents a festive, colourful procession of Swedish children on their way with flowers and gifts to a Norwegian boy. The entrance to the policlinic admits one to a large waiting-room to the right and, to the left, to four small isolation rooms for children suspected of suffering from some infectious disease. Above the corridor on the ground floor are three examination



Fig. 3. The hall with ceramic relief.

rooms, a laboratory for routine examinations, a sterilization room etc. Ordinary patients from the town and country districts come to the polyclinic in the morning, and in the afternoons its rooms are employed as a control station for infants and young children.

From the hall on the ground floor we pass to the right to a lecture room with sitting accommodation for 70, and in connection with this room there is another room for waiting patients and educational material.

In the same building on the first floor and facing the street are several rooms including the Professor's office, a secretarial room, a large library, a reading-room for students, a conference-room, and four doctors' offices. Above the corridor on the same floor are the hospital's main laboratory and two rooms intended for research.

The main hospital is a six-storeyed building which begins with the hall already referred to. From it is a door to the students' cloakroom and to the tunnel connecting the hospital with the other departments of Haukeland Hospital. Just within the hall are the reception room and examination room for patients which give access to the lift and stairs. The other rooms further in



Fig. 4. A four-bed room in the ward for older children (girls).

on this floor are cellar rooms because of the steep character of the ground on which the hospital is erected. Here are to be found various engine rooms, accommodation for oxygen cylinders and shafts for refuse and dirty linen etc. On the first floor of the main building are the hospital's office, the Matron's office and private quarters, a small radiological department, and an entirely modern kitchen. On the same floor space is provided for electrocardiographic and basal metabolism examinations and for a perfectly modern dentist's office. The second floor is given over to the Department for Child Psychiatry with 11 beds in two-bed rooms, an office for the doctor in charge of this department and an assistant, accommodation for a psychologist, for testing, for a curator, a day-room and play-rooms for the patients belonging to this department. Facing east and with an exit from the corridor is a large play-room and a covered loggia leading to two playgrounds. These playgrounds are intended for all the patients who are up and about.

On the third floor are 22 beds for older children (from 5 to about 14 years). The department for older children is in two

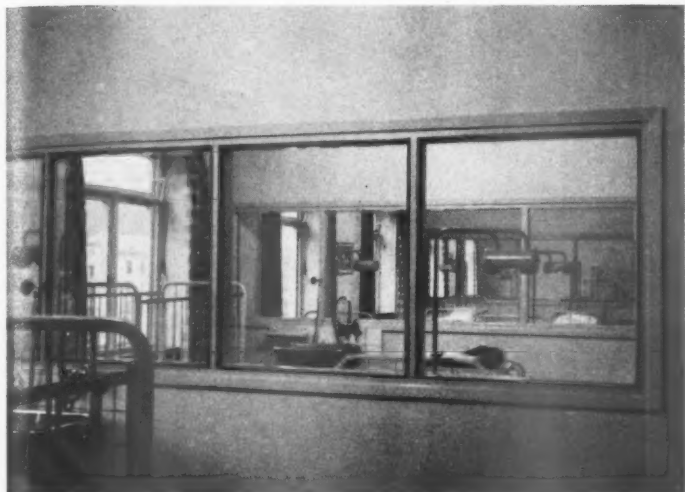


Fig. 5. A two-bed room in the department for small children.

halves, one for boys and one for girls. On the fourth floor there are 24 beds for younger children (from 1 to 5 years).

All the patient's rooms face south. Most of them are two-bed rooms, but there are a few four-bed rooms in the department for older and younger children. With the exception of the rooms in the Department for Child Psychiatry, the walls facing the corridor are of glass as are also the partitions between most of the rooms in order that the nurses may have a comprehensive view of their charges. There is of course no glass wall between the wards for boys and girls. Facing south-west on the floors occupied by the patients, all the departments have a large play-room from which there is an exit to an open balcony carefully fenced in. Facing north, on the medical floors are conference-rooms, two one-bed isolation wards and the necessary annexes such as rinsing-rooms, bathrooms, lavatories and a large modern treatment-room with a sterilizer, wardenroom, a cloak-room and a tea kitchen. A food lift from the hospital's kitchen connects it with the various tea kitchens where the food is placed on a heater till it is served.



Fig. 6. The clinic seen from the north. To the right the two-storied building with polyclinic, offices and laboratory. In the front the main building. To the left is seen the isolation department.

On the east side of the department for older children, i. e. on the third floor, is the Isolation Department which is a one-storied wing facing south and north and furthest east of the building. Thanks to the steep slope on which the hospital is built, this wing has an entry of its own to all the patients' rooms facing east. Each of these rooms is provided with its own bath and W.C. They are designed with a view to the complete isolation of infectious cases. Three smaller rooms in this department face south and are designed for cases of tuberculosis. This small department has its own entrance and exit and its park or open air verandah.

The Infants' Department, with 22 beds and a room for a sick mother with child is on the top storey, i. e. the fifth floor. Here four separate boxes are arranged around a dressing-room. Fresh air is conducted to the boxes from the ceiling, and the used air travels through slits in the door leading to the dressing-room in such a way that the current of air will always pass from the boxes and out. Several of these boxes are provided with incubators, and

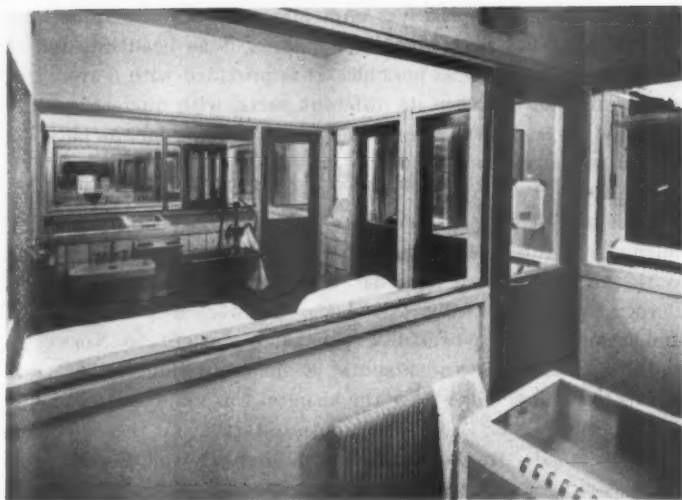


Fig. 7. A view through the department for infant. In the front to the left the dressingroom with four boxes around. In the box in the front an incubator.

oxygen is led to several rooms through piping uniting them with oxygen cylinders in the cellar floor. The Infant's Department is of course provided with a perfectly modern milk kitchen and a room for mothers who suckle their babies.

In each of the four upper storeys there are one private room for the ward sisters and two two-bed rooms for women who suckle; there is accommodation for 12 mothers altogether as well as a drawing-room, a lunch-room and a tea kitchen for them.

In addition to accommodation for mothers there are altogether 92 patients' beds in the hospital. Needless to say, costs have not been counted in making the Children's Hospital first class in every respect. The equipment of the rooms is very suitable throughout the building and the technical material is altogether modern. The sterilizer and kitchen fittings etc. are of stainless steel, sanitary equipment is chromium-plated, and the doors of mahogany or light birch. As one passes from one to another of the more than

400 rooms in the hospital it is impossible to escape the impression that nothing has been spared in making it as beautiful and as modern and practical as possible. It is provided with a system of communication between its different parts, with modern ventilation, and a very clever arrangement for signalling for the patients, as well as many other technical devices.

In 1950, *Tidskrift for Den Norske Lægeforening* (Journal of Norwegian Medical Association) published an editorial article stating that this was a remarkable year for Norwegian pediatrics. With the two modern pediatric University hospitals in Oslo and Bergen, providing fully 200 beds, Norwegian pediatrics had undergone a very powerful expansion of benefit to Norwegian children, to medical students, and to doctors wishing to specialize in this discipline. Ever since the hospital was inaugurated on May 31, 1950, by H. R. H. Crown Princess Märtha, all the beds have been occupied. In the form of a children's hospital designed to serve coming generations, it is a boon to the whole nation. Here it stands in Western Norway, an intensely active body meeting the imperative claims made on it by the community.

The Children's Hospital is surrounded by beautiful scenery and is provided with a charming park. In front, facing south, stands the beautiful sculpture: Mother and Child, the work of the Swedish artist, Ivar Jonsson. But the hospital itself, standing as it does as a monument in itself, not merely of dead stone and cement, is a living witness to its daily service to man. The Swedish nation could hardly have chosen a better Freedom Gift to its brother in the west than just this: A shield and aid for young Norway.

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Barneklínikken
Bergen, Norway.

CASE REPORTS

Meconium Ileus and Hirschsprung's Disease

by

TH. EHRENPREIS

(From the Kronprinsessan Lovisa's Children's Hospital, Stockholm).

Meconium ileus is characterized by stagnation of inspissated meconium in the distal portion of the ileum. Proximal to this the ileum is dilated whereas the terminal portion of the ileum and the entire colon has an extremely small caliber (microcolon). At the site of stagnation the meconium is puttylike and inspissated and very difficult to remove from the intestinal wall, which closes around small fragments of it in the pre-terminal portion of the ileum. The terminal portion of ileum and the whole colon are practically empty. Proximal to the obstruction the size of the ileum gradually increases to a more or less pronounced dilatation. This portion of the intestine contains large amounts of almost normal-looking meconium, not unlike the condition found above an anal atresia.

In the past there have been two main ideas on the cause of this peculiar condition:

1. Primary changes in the intestines, causing stagnation and inspissation of meconium.

Congenital dilatation of the ileum (1) (in analogy with megacolon) and congenital narrowing of the colon (2) (in contrast to megacolon) have both been suggested as causes for meconium ileus at a time, when megacolon was considered to be a congenital dilatation of the colon. Neurogenic disturbance of intestinal motility (3—4) has also been postulated, but not demonstrated.

2. Primary changes in the composition of meconium, causing stagnation with dilatation of the intestine proximally and atrophy of disuse distally.

Deficient admixture of bile with meconium has been postulated in cases with demonstrable (5—6) or hypothetical (7—8) changes in the liver.

In 1905, LANDSTEINER (9) reported the first case of meconium ileus with fibrocystic changes in the pancreas; the latter were considered by LANDSTEINER to be the probable cause of a deficient pancreatic secretion

with inspissation of meconium, resulting in meconium ileus. Similar cases were later described by other authors (10—11).

In 1938 and 1944 DOROTHY ANDERSEN (12) and FARBER (13) published comprehensive reports on fibrocystic disease of the pancreas, demonstrating a close connection between this disease and meconium ileus. These studies have been corroborated by other authors (14—17). The conception of meconium ileus as being the earliest clinical manifestation of fibrocystic disease of the pancreas has been well substantiated and generally accepted. Actually, there seems to be no room left for other interpretations of the pathogenesis of meconium ileus.

The reason for reviewing this question is the recent observation of a case of meconium ileus of different origin.

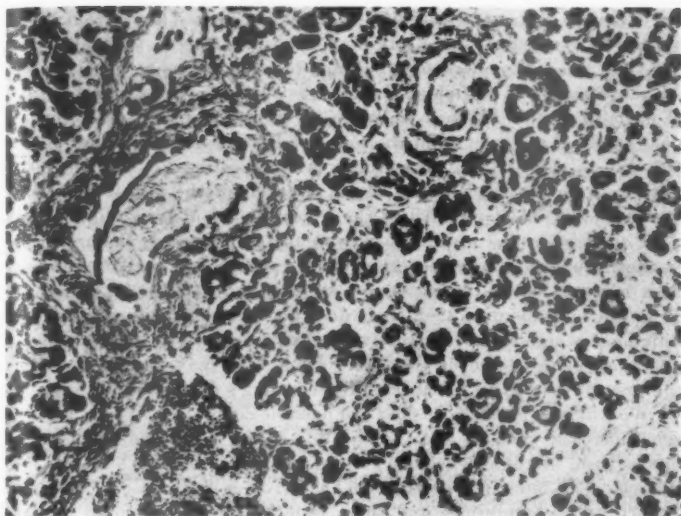
Case report. A female infant was admitted at the age of 3 days with a history of vomiting since birth. She was the fourth child of healthy parents; three siblings were also in good health. The mother's pregnancy had been uneventful and delivery was normal. The baby failed to pass meconium and had no further bowel movements. Vomiting of bile-stained material began almost immediately after birth and abdominal distension developed.

Clinical examination revealed marked abdominal distension. A barium enema showed a typical microcolon and gaseous distension of the small intestine.

Operation disclosed the typical gross pathology of meconium ileus. The upper ileum was greatly distended. Distally the size decreased gradually and the terminal portion of the ileum and the whole colon were extremely hypoplastic. The contents of the pre-terminal portion of ileum were greyish and sticky and were removed with difficulty through an enterotomy. The upper ileum contained large amounts of meconium of normal appearance, which was removed through another enterotomy. The terminal ileum and entire colon were empty except for residues of the barium enema. After clearing of the intestinal passage and closure of both enterotomies the abdominal wall was closed. Analysis of meconium from the terminal ileum revealed absence of tryptic activity.

Post-operative treatment consisted of pancreatin, penicillin and colonic irrigations, but the bowels still failed to move. After one week abdominal distension reappeared and after two weeks the condition became critical. It was decided to perform an ileo-transversostomy. At operation, however, a tremendously dilated loop of the distal ileum was found to be adherent to the abdominal wall; this was incised through the peritoneum. The ileostomy thus performed was left and the operation discontinued.

After the second operation the child suffered from heavy losses from her ileostomy and her condition slowly deteriorated. At the age of 6 weeks she was discharged because of varicella-infection of the ward and



Photomicrograph of pancreas.

sent to a local hospital for infectious disease in the north of Sweden, where she died about one week later.

Autopsy revealed no material changes in the gross pathology compared with the operative findings. The abdominal viscera were removed and microscopic examination (Prof. Bergstrand) gave the following result: The pancreas showed a focal increase in connective tissue, inspissation of eosinophilic secretion in the acini and ducts, distension but no true cyst formation and slight interstitial infiltration with inflammatory cells. The picture corresponded to an early stage of fibrocystic disease of the pancreas. The dilated part of the small intestine showed no abnormality of the myenteric plexus but *from the narrow terminal part of ileum on and throughout the entire colon no ganglion cells could be found.*

Discussion

These are findings of a very great interest. Microscopic examination reveals two possible explanations to the intestinal obstruction present. On the one hand there are pancreatic changes, which in connection with the gross pathology found would justify a diagnosis of meconium ileus. On the other hand there is an agenesis of the myenteric plexus within

the terminal ileum and throughout the colon. As we know from recent studies by WHITEHOUSE & KERNOHAN (18), BODIAN *et al.* (19) and SWENSON (20), this is the characteristic lesion found in Hirschsprung's disease. Although the gross pathology of this case was one of microcolon and not of megacolon the difference seems to be one of quantity rather than of quality. It is apparent from the series of Hirschsprung's disease quoted (18—20) as well as from the author's personal series (21) that the distal narrow segment, which is the site of agenesis of the myenteric plexus, varies greatly in length. All of the series quoted above comprise cases with agenesis of the myenteric plexus up to the splenic flexure. Prior to these studies of the myenteric plexus in megacolon, similar cases have been reported with a distal narrow segment extending as far proximally as the hepatic flexure (22—27). It does not seem to make any material difference whether the obstructive segment comprises the distal colon only, half of the colon or the entire colon. We may, therefore, classify the present case as an instance of Hirschsprung's disease.

We will now have to consider the possible connection, if any, between the pancreatic changes and the agenesis of the myenteric plexus found in this case. A coincidence of two separate malformations has to be considered. The intestinal obstruction, however, is fully accounted for by either of these conditions and there seems to be no reason to presume a mere coincidence of two different conditions as rare as fibrocystic disease and Hirschsprung's disease. Agenesis of the myenteric plexus can only be interpreted as a primary failure of development and not as due to changes in the pancreas. These, on the contrary, could be secondary changes, due to reflux from the intestine, obstructed by agenesis of the myenteric plexus.

An extensive search of the literature has failed to reveal any reports of cases of meconium ileus showing pancreatic changes as well as agenesis of the myenteric plexus. Only circumstantial evidence for the suggested sequence of events has been found.

1. A number of cases of intestinal atresia showing fibrocystic changes in the pancreas have been reported (12, 15, 17). It has been suggested that the intestinal atresia might be due to resorption and organization of inspissated meconium (17), i. e., secondary to the pancreatic abnormality. This is not the ordinary conception of the origin of intestinal atresia. The combination of intestinal atresia with pancreatic changes is very interesting from the converse point of view and might be a more common occurrence than we realise at present.

2. Cases of meconium ileus with no pancreatic abnormality have been reported (5, 30). No reports of examination of the myenteric plexus are given.

3. PERROT & DANON (28) and ZUELZER & WILSON (29) have reported two cases, showing the gross pathology of meconium ileus as well as

changes within the myenteric plexus. Examination of the pancreas is not reported in either of these cases. In the case of PERROT & DANON the myenteric plexus of the terminal ileum, the ascending and the transverse colon was hypoplastic. The upper part of the small intestine and the distal part of colon showed a normal amount of ganglion cells.

ZUELZER & WILSON report 11 cases of functional intestinal obstruction in infancy with agenesis of the myenteric plexus supplying the obstructive segment of the bowel; this series is described as a new clinical entity. Ten of these cases seem to be typical cases of Hirschsprung's disease and one (Case 9) a case of meconium ileus with agenesis of the myenteric plexus supplying the terminal ileum and the entire colon. The series is suggestive of a connection between these two diseases.

Conclusions

Without questioning the close connection generally accepted between fibrocystic disease of the pancreas and meconium ileus it seems justified to state that some cases of meconium ileus are due to an extensive agenesis of the myenteric plexus, and that these are virtually cases of Hirschsprung's disease. These cases may or may not show secondary change in the pancreas. The proportion of these two types of meconium ileus cannot be settled as long as studies of the myenteric plexus in meconium ileus are rare.

Summary

A case of meconium ileus showing both agenesis of the myenteric plexus to the terminal ileum and the colon and fibrocystic changes of the pancreas is reported. It is suggested that agenesis of the myenteric plexus is the cause of the intestinal obstruction in this case, and that the changes found in the pancreas might be due to reflux. The present case of meconium ileus is, therefore, virtually a case of Hirschsprung's disease. This might be a more common occurrence than we realise at present.

TH. EHRENPREIS: *Ileus méconial et la maladie de Hirschsprung.*

On rapporte un cas d'ileus méconial montrant l'agénésie du plexus mésentérique dans la partie terminale de l'ilion et dans tout le colon ainsi que des transformations fibrocystiques du pancréas. On pense que l'agénésie du plexus mésentérique est la cause matérielle de l'obstruction intestinale dans ce cas, et que les transformations trouvées dans le pancréas peuvent être dues à un reflux.

Le présent cas d'ileus méconial est donc virtuellement un cas de maladie de Hirschsprung.

TH. EHRENPREIS: *Meconiumileus und Hirschsprung'sche Krankheit.*

Es wird über einen Fall von Meconiumileus bei Agnesie des Plexus myentericus im Bereiche des unteren Ileums und des gesamten Colons sowie fibrocystischen Pancreasveränderungen berichtet. Vermutlich dürfte die fehlende Entwicklung des Plexus myentericus in diesem Falle die Hauptursache des Darmhindernisses sein und die beobachteten Veränderungen im Pancreas sind möglicherweise Folgen einer Rückstauung. Der vorliegende Fall von Meconiumileus ist somit scheinbar ein Fall von Hirschsprung'scher Erkrankung.

TH. EHRENPREIS: *Ileo meconial y enfermedad de Hirschsprung.*

Se da un caso de ileo meconial que presentaba agenesia del plexo mientérico en la porción terminal del fleon y en la totalidad del colon, asi como una fibrosis quística del páncreas. Se sugiere que la agenesia del plexo mientérico es la causa material de la obstrucción intestinal en este caso, y que las alteraciones pancreaticas puedan ser debidas a un estasis por reflujo. El presente caso de ileo meconial es pues un verdadero caso de enfermedad de Hirschsprung.

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Wolff-Parkinson-White (W. P. W.) Syndrome in a One Year Old Child

by

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Only isolated instances of the W. P. W. syndrome in infants have been reported in the literature. From Scandinavia cases of the W. P. W. syndrome have previously been published by CHRISTENSEN (1944), JÖRGENSEN (1945), MANNHEIMER (1945), and SKATVEDT (1948). A summary of all cases of pre-excitation in children published prior to 1945, including two new cases, has been reported by LIND (1945). At the Children's Hospital in Gothenburg such a case has been followed up in a girl from the age of 1 to 10 years.

The child was first admitted in 1937, at the age of 1 year, with rickets and tetanic spasms. Examination revealed no cardiac abnormalities. Repeated electrocardiograms showed the typical W. P. W. pattern. (Fig. 1). The pulse rate was 130 per minute. Similar changes are also found in tetany, but the clinical course confirmed the diagnosis of W. P. W. syndrome.

During the following six months the patient was followed up in the outpatient department. Repeated electrocardiograms were unchanged. Only on one occasion could a systolic murmur be heard. The child developed normally, and underwent without complications two major operations, mastoidectomy and appendectomy.

In 1944, at the age of 8 years, she was sent to hospital by the school doctor because of shortness of breath on climbing stairs. There were no other signs of cardiac decompensation. Auscultation revealed a harsh

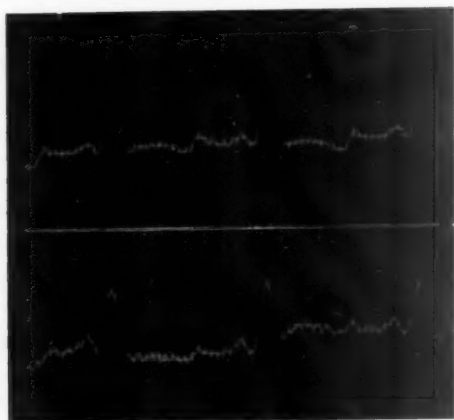


Fig. 1.

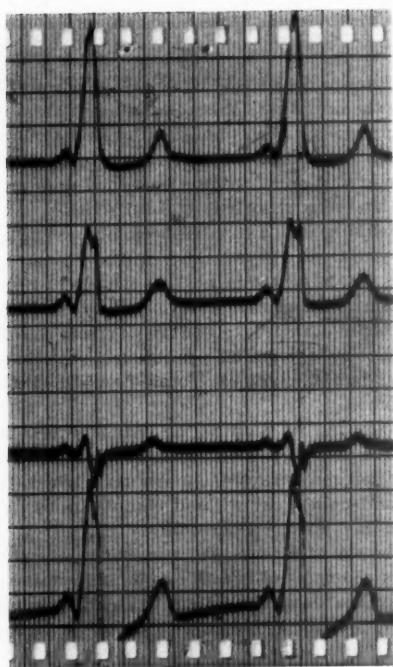


Fig. 2.

systolic murmur with its maximum over the apex. P_2 was accentuated. Pulse rate was 70 per minutes. X-rays showed a normal sized heart. ECG still showed the typical W. P. W. pattern.

Since 1944 the patient has been quite well. She takes part in sports and only occasionally complains of shortness of breath and tiredness.

In 1946, at the age of 10, whilst out playing one day, the girl stated that everything went black, and she threw herself to the ground. Her heart pounded, and she had to be helped home to bed. She had tachycardia for 4-5 hours, but the pulse rate was not counted. The following day she came to the hospital. Examination showed the same E. C. G. changes as earlier. (Fig. 2).

Since this attack the patient has been under control at the outpatient department and feels quite well.

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Coxsackie Virus Infection¹

Report of two cases

by

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Poliomyelitis has for long been an important problem. It was therefore of very great interest when, in 1948, DALLDORF and SICKLES isolated from the faeces of a case of poliomyelitis a new virus, now called the Coxsackie virus (C virus).

¹ Paper read at the Meeting of the Pediatric Section of the Swedish Medical Association, Sept. 15, 1950.

CURNEN, SHAW, and MELNICK confirmed this discovery and succeeded in isolating the organism in patients with non-paralytic poliomyelitis and meningitis. They observed a wave of non-paralytic cases preceding a typical poliomyelitis epidemic; in the former cases, this virus was isolated mainly during the first stage. It was believed by CURNEN and his co-workers that two different infecting agents were present and that the mild, non-paralytic form was caused by the newly discovered C virus.

In Sweden, GARD (1949) recovered the C virus from the faeces, throat and cerebrospinal fluid of several patients with the clinical picture of paralytic or non-paralytic poliomyelitis. (These cases were reported by LINDAHL at a meeting of the Society of Internal Medicine in Stockholm in 1950.)

We are aware that, epidemiologically, the new virus is very similar to the poliomyelitis virus. This permits the inference that these two disease-producing organisms very often occur together in epidemics. Serological studies nevertheless show that there is an evident difference between the poliomyelitis virus and other known viruses. We know that it is entirely uninfluenced by antibiotics and by sulphonamide drugs and that patients with similar C virus infections produce specific antibodies. These antibodies, which have the ability to neutralize the isolated virus, develop mainly during the convalescent stage. It was this antibody which was used by GARD in the Swedish investigation. He obtained positive reactions in 30—50 per cent of examined serum. There is thus good reason to presume that C virus infection is quite common in this country. GARD's material consisted of patients admitted to hospital as non-paralytic poliomyelitis or meningitis patients. The C virus was recovered from the faeces, throat and cerebrospinal fluid and the serum gave positive reactions.

The symptomatology is not yet fully clear. It appears, nevertheless, to be fairly uniform. The onset is acute, with high fever, nausea and vomiting, sore throat, headache, slight stiffness of the neck and, in some cases, muscle pains. In the majority of cases the C. S. F. findings are positive, with slight pleocytosis. Since it has now been possible to isolate different C virus strains, one of which appears to be more neurotropic and the other more myotropic, it is understandable that considerable variations in the intensity of the different symptoms may be anticipated. It is often difficult to make a differential diagnosis between a C virus meningitis and meningitis of other origin. It has also been possible to isolate the C virus in myositis of the Bornholm disease type. Many mixed infections have been observed and the aetiological significance of the respective viruses has not yet been elucidated.

The investigations mentioned in the foregoing were made on series taken during widespread epidemics. The two cases of C virus infection reported in the following were treated at the Sachs' Hospital for Children

in Stockholm. The first case occurred during a period (January) when there was no known epidemic. Nor had any case presenting a similar picture occurred in the patient's surroundings. The main feature of the first case was meningeal irritation, whereas myositic discomforts predominated in the second case.

Case 1. A 7 $\frac{1}{2}$ year old girl, previously healthy with the exception of intermittent stomach pains of somewhat diffuse nature (pain around the umbilicus, colicky in type, without vomiting but followed by an exanthema). Became ill in January 1950 with stomach pain of the same type as earlier. The pain disappeared after a few days. 5 days later her temperature rose to 40° C. She had no evidence of a throat infection nor pain in her stomach, but complained of severe headaches and a sore throat. The latter lasted about three days. Thereafter, there was spontaneous improvement without treatment. The headaches were so severe that the patient complained loudly when turning her head. Magnesium salicylate was used and helped a little initially but later had no effect at all. The temperature fell to 37° C in 24 hours and remained between 37° and 38° C for the next few days. She attended the outpatient department for the first time 7 days after the onset of her illness. She then complained of pain on bending her neck and there was some redness of the posterior part of the pharynx. She was admitted to the hospital as a possible case of meningitis. After admission her throat was moderately red but there was no neck stiffness. Reflexes normal. No headache. Lumbar puncture showed slight pleocytosis and Pandy sign. There were no other symptoms; temperature 37° C; the throat, faeces and C. S. F. were examined for possible virus infection. Remained in hospital ten days. No discomforts; temperature normal or subfebrile. General condition satisfactory. The diagnosis C virus infection was based both on the fact that this virus could be isolated from faeces taken during the acute stage of the illness, and through neutralizing tests with the patient's serum, which were positive 14 and 21 days after onset of illness. On both occasions the value was 256. (Prof. S. Gard). The clinical picture was similar to previously described C virus infections. There was a moderate pleocytosis. It is impossible to state with certainty whether during the acute stage of the illness at home there had been any real neck stiffness or only pseudoneck stiffness caused by the severe headaches.

Case 2. A 4 $\frac{1}{2}$ year old boy who had earlier been healthy, with the exception of frequent upper respiratory tract infections. After returning from the country at the end of the summer, he complained of pains in his legs for the first two days. On the 3rd day his temperature was 40° C and remained at this level for a further two days. He was then free from discomforts, lively and active for five days. On returning home from playing outdoors on the 10th day he limped slightly. His mother took no notice of this symptom in view of his activity during the day. How-

ever, he woke in the night, complained of pain in his left leg and then slept very uneasily. The following day he refused to bear weight on his leg. He was brought to the outpatient department; on examination he still refused to bear weight on the leg. Examination revealed no other definite symptoms and the patient was therefore sent home. However, he was brought in again later in the evening since, on waking from sleep he had started to vomit violently. He also complained of slight headache; the pain in his leg seemed to have disappeared. Examination showed very slight reddening of the fauces and a slight decrease in the patellar reflex on the left side. After about an hour the reflex once more became normal. Neurological examination revealed nothing pathological. During the first two days his temperature was 38.5–39.0° C. He was subsequently afebrile and had no constitutional symptoms. He was discharged from hospital after 11 days with no residual discomforts. Specimens from the throat, faeces and C. S. F. were examined virologically. C virus could be isolated from the faeces specimen taken the day after admission. C virus antibodies were present in the serum; the neutralizing index was determined. Lumbar puncture on admission showed a positive protein reaction (Pandy and Nonne +) but no cells were found.

The cases reported here confirm the fact that the infection is relatively mild and regresses without specific therapy.

Summary

An account is given of two cases of Coxsackie virus infection in children. The patients recovered without specific therapy and were discharged from hospital entirely free from symptoms.

E. A. DAHLSTRÖM: *Infection de virus du Coxsackie.*

Une exposée est donnée de deux cas des enfants avec infection de virus du Coxsackie. Sans thérapie spécifique les malades ont été guéris et ont été délivrés totalement des symptômes.

E. A. DAHLSTRÖM: *Über die Infektion mit Coxsackie-Virus.*

Es wurde über zwei Fälle von C-Virusinfektionen bei Kindern berichtet. Die Patienten genasen ohne spezifische Therapie und wurden völlig symptomfrei aus dem Krankenhause entlassen.

E. A. DAHLSTRÖM: *Infección por virus Coxsackie.*

Se relatan dos casos de infección por virus C en niños. Los pacientes se restablecieron sin terapéutica específica y fueron dados de alta del hospital enteramente libres de síntomas.

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Congenital Hydrocephalus in a Newborn Infant — Epidemic Hepatitis in the Mother in the Second-Third Month of Pregnancy

by

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Since GREGG announced his discovery in 1941 (1), German measles in the mother during the first trimester of her pregnancy has become one of the accepted factors in the aetiology of congenital malformations.

Since this discovery, several publications have appeared in Australia, America and Europe dealing, in some instances, with a very great number of malformed children in whom this factor was demonstrable.

According to these publications it seems evident that the degree of severity of an attack of German measles in the mother is of subordinate importance; rather it is the date of the appearance of this disease which determines the degree and extent of the damage to the foetus. The frequency with which malformations occur is over 90 per cent, if the mother falls ill during the first four months of her pregnancy—the organogenetic period of the foetus. This frequency is approximately 100 per

cent, if she falls ill during the first two months. The distinctive defects in the child born of a mother infected with German measles at this stage are cataract, heart disease, deafness, defective teeth, microcephalus and oligophrenia.

Within this period it is, in particular, the week of foetal life in which the mother is infected that determines which of these defects may occur in the child. In addition to these lesions, the child may also be marked by less characteristic evidence of injury to the brain.

We can assess the frequency with which malformations in the child occur as the result of German measles in the mother partly by examining the progeny of women who state that they have suffered from this disease during pregnancy and, conversely, partly by questioning the mothers of defective children.

Naturally, there has been considerable virus diseases other than German measles in connexion with such investigations. It has been noticed that measles, mumps, chickenpox and influenza in the mother at the time of her pregnancy have led to defects in her child. Even the common cold (2) has been cited as a factor of importance in the critical organogenetic period.

While many such cases have been published in association with German measles, little has hitherto been published about the other virus diseases and the part they may play in the development of defects in children. The largest number of cases seems to have been published by SWAN and his associates (3). Their cases, collected in Australia, included 18 women who suffered from measles during pregnancy; one aborted and three gave birth to defective infants. Six women, who had had mumps, gave birth to defective infants, and one of two women who had had chickenpox during pregnancy gave birth to a defective infant. It may well be difficult to achieve any degree of precision if we are to accuse the common cold as being a causal factor. For during the cold season in many countries the common cold occurs with such frequency that many pregnant women will not escape it. Its tendency to relapse on account of poor acquired immunity, as distinct from most other virus diseases, means that the expectant mother will usually ignore it and will find it difficult to recall times of infection when she is subsequently asked the diseases from which she has suffered during pregnancy.

An attempt has been made, in connexion with the following case, to find out if other reports have appeared of women who suffered from acute hepatitis during pregnancy and who gave birth to defective infants in consequence. No mention is made of this subject in the pediatric and neurological textbooks and journals which I have been able to consult.

In an investigation of wide scope in Sweden covering the period 1945-1947, GRÖNWALL and SELANDER (4) have tried to throw light on the part played by the various virus diseases during pregnancy. Among

their 14 926 mothers examined there were 29 who had been jaundiced during pregnancy. Only one of them, jaundiced in the third month of pregnancy, had given birth to a defective infant suffering from cleft palate. Among 282 mothers giving birth to infants with congenital lesions were three who had suffered from hepatitis during pregnancy. The mothers of two infants suffering from mongolism had developed hepatitis in the third and eighth month; the third case was that of the cleft palate infant already referred to. No records of other cases could be found.

Case History. (Reference No. 82/50.) A day-old male infant was admitted to the University Pediatric Hospital on June 28, 1950. No family history of interest, and particularly no record of any cases of congenital malformations, diseases of the nervous system etc. Parents healthy. The mother, a primigravida, aged 30, had been confined to bed by jaundice for three to four weeks while in the second and third months of pregnancy during which she had otherwise been well and under regular medical supervision. She was admitted to the Maternity Hospital four days after the expected date of confinement. As the clinical and radiological evidence was suggestive of a hydrocephalic infant, and because of the mother's short pelvic measurements, lower segment Caesarean section was undertaken. Some difficulty was experienced in the delivery of the large, definitely hydrocephalic head whose circumference at the widest was 46 cm. Weight at birth 4 570 g, length 55.5 cm. The infant's general condition was good.

On admission to the University Pediatric Hospital, no defects other than the marked hydrocephalus were found. Complexion normal, as were turgor and tone. Subcutaneous layer of fat well developed. Crying satisfactory, movements free and powerful. *Caput:* Face well-formed and proportioned. Cranium large and prominent, with eyes deep-seated, far back in the head, and somewhat "depressed," with the result that a 2 mm wide free rim of the sclerae could be seen above. (Fig. 1). The covering skin was darker than that of the face and rest of the body, with well-developed venous markings. Here and there the outlines of the cranial bones were comparatively soft and prominent. The sutures were palpable, one fingerbreadth in width. The bones were firm and sharply defined, and the parietal bones could be easily displaced. The occipital bones projected like a ridge while the lambdoid suture formed a wide open furrow from the posterior fontanelle to the base of the skull. The soft areas were fluctuating but not abnormally tense. In other respects an ordinary physical examination revealed nothing noteworthy.

During the following days slight icterus neonatorum set in (serum colour 22). On the second day some small cramp-like twitchings developed, being most marked in the left arm and leg and ceasing after treatment with small doses of fenemal. They did not recur when this treatment



Fig. 1.

This photograph of the head taken post mortem shows its marked hydrocephalic feature and gives some impression of the microphthalmus.

was discontinued after six days. The general condition, which had been quite good on admission, became gradually worse. During the first 14 days the weight fell to about 4 000 g at which level it subsequently remained fairly constant. The circumference of the head increased gradually to 50 cm when the infant was five weeks old, and it remained unchanged during the last few weeks. In spite of hot bottles in the bed, the temperature remained persistently low. Flaccidity steadily increased, and feeding became more and more difficult, and vomiting more persistent. Death occurred at the age of eight weeks.

Special examinations:

An examination of the eyes on June 30, 1950, showed small interpalpebral fissures and very deep-seated eyes. Corneae about 10 mm wide. Clear media. Fundus oculi could be seen with about +10 D, i. e., considerable hypermetropia. The colour and boundaries of the nasal part of the optic discs normal, whereas the temporal section was pale and deep on both sides, but without excavated margins. Orientation of the eyes parallel. His eyes did not follow light, but he closed them again when light was suddenly directed on them. Conclusion: slight microphthalmus with proportional cornea.

When the ophthalmoscopic examination was repeated two days before death, the optic discs were seen to be strikingly white, almost shining, with a sharply defined pigmented boundary. Beyond this there was a greyish zone which in its turn presented pigmentation with a radius almost double that of the optic disc. There was marked pulsation of the vessels in both discs. Fundus oculi were pale. Unfortunately these findings could not be checked by an ophthalmologist.

Lumbar puncture on July 1 and August 2, 1950, yielded on both occasions only about 3 ml of a clear, yellow fluid. More than this quantity could not be withdrawn on either occasion, and the planned air-encephalography had to be abandoned. Puncture of the ventricles was not undertaken.

An electrocardiogram on July 1, 1950, showed relative sinus bradycardia (85—95), a low voltage and less pronounced right axis deviation (95°—100°) than might have been expected in an infant of this age.

On June 30, radiological examination of the skull showed a considerable increase in size, a thin calvarium, and wide and open sutures. On August 29, a repeated radiological examination showed stripe-shaped, densely calcified shadows in the sagittal plane over the median and posterior part of the skull. Those shadows could not be recognized when an exposure was taken in the frontal plane, and because of the very precarious state of the patient it was impossible to take further pictures in order to localize these shadows.

Blood samples taken on July 3 and August 30, 1950, were negative to the dye test (i. e., there was no sign of toxoplasmosis). The infant gave a negative Meinicke and the mother a negative Wasserman reaction. Routine tests on the blood and urine showed nothing pathological.

The *post-mortem* report (No. 282/50—Dr. F. G. Gade's Pathological-Anatomical Laboratory in Bergen) showed the following: Nothing noteworthy in the neck, thorax or abdominal organs. The heart, in particular, was found to be normal, well contracted, and without any noteworthy condition of its valves. Foramen ovale and ductus Botalli closed. When the skull was opened, 1 760 ml of a clear, yellow fluid escaped. After its

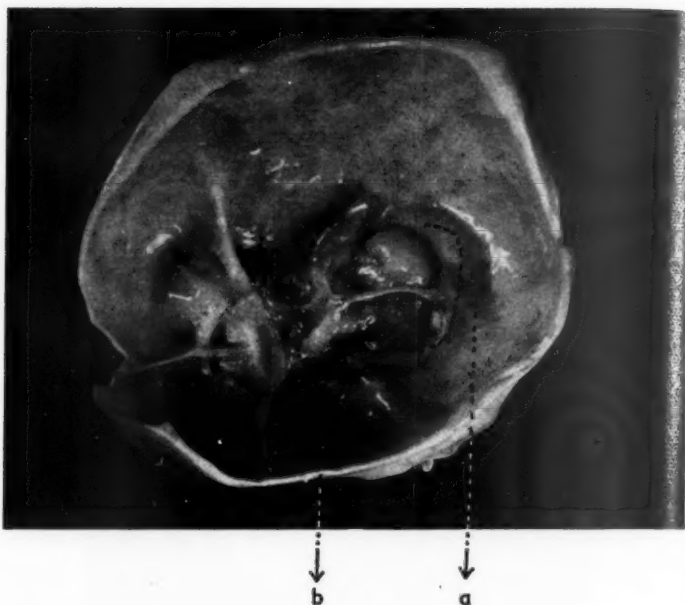


Fig. 2.

This photograph was taken directly after the skull had been opened and after only fluid had been removed from it. The brain is reduced to a small lump lying at the base of the skull. It will be seen that most of it consists of the cerebellum (a) whose shape and size are practically normal. Remains of the cerebrum (b) are seen as a small lump lying in the front of the cerebellum.

evacuation, the brain was seen to be compressed at the base of the skull in which it lay forming a little lump, measuring about 8 by 5 cm. Traces of a falx cerebri were found. The pia mater was intact on the right side, but appeared to be ruptured on the left where the brain substance was damaged. The tentorium was intact, and the cerebellum did not seem to be reduced in size. The dura mater was intact and lined the interior of the skull everywhere.

Inspection of the brain, fixed in formalin, showed that the pons and the medulla oblongata, as well as the cerebellum retained their ordinary shape and appearance. The pedunculi cerebri arose each from one side of the pons (proximal) being about 1/2 cm long and secured to what was left of the cerebrum,—a lump of white brain matter of the size of a walnut.

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(Fig 2). On close inspection it was seen that the right cerebral hemisphere measured 4 by 2 by 1 cm. This formed a bow-shaped structure containing a large central cavity lined with ependyma and constituting the whole of the central part of the cerebrum in which there was no partition. A hint of sulci could be detected on the upper surface of the right cerebral hemisphere. The left cerebral hemisphere consisted of an irregularly shaped lump of brain matter, flat, about the size of a halfpenny, and entering into the structure as part of the wall of this central cavity which was for the most part lined by ependyma. In a rostral direction and in front, the wall of this cavity presented a large defect or gap whose thin walls consisted of pale brain matter lined by ependyma. Above and in the posterior wall of the cavity a lump of brain matter, of the size of a hazel nut, could be seen; its shape was reminiscent of the thalamus. No similar lump could be seen on the left side. The choroid plexus lay at the bottom of the cavity and was yellow in colour. Small traces of the falx and tentorium cerebelli could be seen attached behind to the brain, presenting a flap with a free border.

Conclusion: A considerable degree of hydrocephalus. The cerebrum and brain-stem are represented only by rudimentary remains. It is possible that from the outset there had been an internal hydrocephalus which had ruptured, for a large central cavity was found, and it seemed to be somewhat collapsed.

Discussion

Congenital hydrocephalus is not a common condition. On rare occasions it may depend on an intracranial tumour, but as a rule it is due to infections (syphilis or toxoplasmosis) or to some congenital anomaly. In the present case serological tests for syphilis were negative in both mother and child. From the outset, toxoplasmosis was suspected because of the combination of congenital hydrocephalus with microphthalmus. Two blood samples from the child and later one from the mother all gave negative neutralization reactions for toxoplasmosis (the dye test negative).

In spite of these negative serological reactions, toxoplasmosis was again suspected when a further radiological examination of the patient (when he was seven weeks old) showed calcification shadows which were apparently intracranial. When the post-mortem examination showed that all that was left of the brain matter lay like a little cake at the base of the skull, it was evident that the calcification shadows could not be due to cerebral calcification. The parietal bones were therefore taken out and were shown on X-ray examination to present stripe-shaped calcifications radiating towards the margins of the bones; these were identical with those found in skiagrams of the skull.

Fluid was aspirated from the hydrocephalus directly after death. During the post-mortem examination samples were taken of the brain and of the mucous matter at the base of the skull. No toxoplasma-like structures could be found on the direct examination of this material in spite of several samples being stained in different ways. The cerebrospinal fluid and brain tissue were given by subcutaneous and intraperitoneal injection to seven mice and two guinea-pigs, all of whom were alive and well three weeks after the inoculation. It is therefore certain that the possibility of toxoplasmosis can be dismissed in this case.

The most probable explanation of the congenital hydrocephalus in this case is that it was due to a developmental anomaly. The conditions found are among those which are described as common in children whose mothers have suffered from German measles during the first trimester of pregnancy.

This patient's mother suffered from jaundice during the second and third months of pregnancy. There was nothing in her history to indicate cholelithiasis nor inoculation hepatitis, but on the other hand it was stated that there had been several other such cases at the same time in her home surrounding. Her illness was taken to be a definite case of acute, infectious (epidemic) hepatitis which had run quite a severe course as her illness progressed for a comparatively long time; she had had dark urine, pale motions and obvious jaundice for which she was confined to bed for from three to four weeks.

Apart from this illness, which had occurred during the first trimester of her pregnancy, she had been perfectly fit throughout the whole of it, had been exposed to no trauma nor to the action of the X-rays till she was examined by them, as already reported, four days before her delivery by Caesarean section.

It seems justifiable to put this case on record as one of congenital malformation in a child whose mother had suffered from acute infectious hepatitis in the first third of her pregnancy (the foetus's organo-genetic period). This case is recorded in some detail as no similar case seems to have been published up to date.

Summary

A case is reported of a male infant admitted to the University Pediatric Hospital in Bergen when only one day old. There was marked hydrocephalus and microphthalmus at birth but no other deformities were found. There was no evidence of syphilis or toxoplasmosis. The patient died when eight weeks old.

A post-mortem examination showed a severe hydrocephalus externus (1 760 ml of fluid) and a brain compressed into a small lump at the base

of the skull. The shape and size of the cerebellum, pons and medulla oblongata were normal, whereas the cerebrum was represented by a mass of white brain matter of the size of a walnut. It is possible that the hydrocephalus was originally an internal hydrocephalus, for what was left of the cerebrum presented itself as a sac showing signs of having been ruptured.

The patient's mother had suffered from epidemic hepatitis in the second and third months of her pregnancy during which she had otherwise been perfectly fit, exposed neither to injury nor X-rays. The abnormal conditions in the child, corresponding as they do to the conditions often found in children whose mothers have suffered from some virus disease during pregnancy, are taken to be the outcome of the acute infectious hepatitis from which the mother suffered during the foetus's organo-genetic period.

A. KÄSS: *Hydrocéphalie congénitale chez un nouveau-né. Hépatite épidémique chez la mère pendant les deuxième et troisième mois de la grossesse.*

A l'Hôpital Universitaire Pédiatrique de Bergen, on discute autour d'un enfant male admis à l'âge d'un jour. Il présentait une hydrocéphalie marquée et un microphthalmus des la naissance, sans aucune autre deformation. Aucune syphilis, ni toxoplasmose n'ont pu être mise en evidence. L'enfant est mort à l'âge de huit semaines.

L'autopsie montrait une hydrocéphalie externe (1760 ml de liquide) et le cerveau comprimé en forme de petit gâteau a la base du crâne. La forme et la taille du cérébellum, du pons et de la medulla oblongata étaient normales, tandis que le cérébrum était représenté par une masse de matière cérébrale blanche de la taille d'une noix. Il est possible que cette hydrocéphalie fut d'abord une hydrocéphalie interne, pour la raison que ce qui restait du cérébrum avait la forme d'un sac présentant des signes de déchirures.

La mère de l'enfant avait été atteinte d'une hépatite épidémique pendant les 2^{ème} et 3^{ème} mois de la grossesse, qui sans quoi s'était bien passée, sans aucune exposition ni à des rayons X, ni à une atteinte quelconque. L'état anormal de l'enfant, correspondant aux états souvent trouvés chez les enfants dont les mères ont été atteintes d'une maladie à virus quelconque pendant la grossesse, est pris comme le résultat de l'hépatite infectieuse aiguë dont la mère a souffert pendant la période organo-génétique du foetus.

A. KÄSS: *Kongenitaler Hydrocephalus bei einem Neugeborenen nach Hepatitis epidemica der Mutter in den 2.—3. Schwangerschaftsmonaten.*

Man erörtert den Fall eines neugeborenen Knaben, der nur einen Tag alt in die Universitäts-Kinderklinik von Bergen eingeliefert wurde. Bei

der Geburt bestand ein ausgeprägter Hydrocephalus mit Mikrophthalmus ohne sonstige Deformitäten. Es fanden sich keine Anhaltspunkte für Syphilis oder Toxoplasmose. Der Patient starb im Alter von 8 Wochen.

Die Obduktion ergab einen bedeutenden Hydrocephalus externus (Flüssigkeitsmenge: 1760 cc) mit Komprimierung des Gehirns auf Semmelgrösse an der Schädelbasis. Grösse und Form von Kleinhirn, Pons und Medulla oblongata waren normal, während das Grosshirn in Form einer walnussgrossen Masse weisser Gehirns substanz vertreten war. Möglicherweise bestand ursprünglich ein interner Hydrocephalus, nachdem der Grosshirnrest sich als ein Sack mit Anzeichen einer vorangegangenen Ruptur erwies.

Die Mutter des Patienten hatte eine Hepatitis epidemica im 2.—3. Monate ihrer Schwangerschaft, während welcher sie sonst völlig gesund und weder einem Trauma noch Röntgenstrahlen ausgesetzt war. Der abnorme Zustand des Kindes, der den häufig beobachteten Veränderung bei Kindern entspricht, deren Mütter während der Schwangerschaft eine Viruskrankheit durchmachten, wird hier dem Ergebnis der akuten infektiösen Hepatitis zugeschrieben, an der die Mutter während der Organentwicklungsperiode des Foetus litt.

A. KÅSS: *Hidrocefalia congénita en un recién nacido cuya madre había tenido una hepatitis epidémica entre el 2º y 3º mes de embarazo.*

Se trata de un recién nacido de un día de edad que ingresó en la clínica pediátrica de la Universidad de Bergen y que presentaba una hidrocefalia junto a una microftalmia muy marcada, no acompañada de ninguna otra malformación. No había signos evidentes de sífilis o toxoplasmosis. El niño murió cuando tenía ocho semanas.

La madre de este niño había estado afecta de una hepatitis epidémica entre el segundo y tercer mes del embarazo, aparte de ello tenía buena salud y no había sufrido ningún traumatismo ni había sido irradiada.

Las alteraciones del niño corresponden al cuadro clínico encontrado muchas veces en niños cuyas madres han tenido alguna infección a virus durante el embarazo y en este caso probablemente la hepatitis epidémica aguda de la madre tenida en el período organogénico fetal ha sido la responsable de la malformación.

Litteratur

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PROCEEDINGS OF PEDIATRIC SOCIETIES

Proceedings of the Section for Pediatrics and School Hygiene of the Swedish Medical Society.

Meeting, September 15, 1950.

Birgitta Werner: Two cases of adrenal cortex insufficiency in infants.

Case 1: Fully developed male child, born 11.4. 1941. Parents and their other children healthy. Admitted to hospital at an age of 17 days, owing to projectile vomiting and loss of weight. At admission, the appearance suggested a pylorospasm. Ventricular x-ray negative. On suspicion of relative intestinal obstruction, transferred to surgical clinic. Explorative laparotomy, no findings. Died about 10 days after operation, from infection. Autopsy: enlarged adrenals — weight 18 g together (normal value 5 g) — with a gyrated surface suggestive of cerebral convolutions. Microscopy: cells deficient in lipoids.

Case 2: Fully developed male child, born 1.5. 1950. Breast-fed, only child. Parents healthy. After returning home from the Maternity Hospital, successive loss of weight in spite of an adequate diet. In connection with a slight common cold, refused to eat, tended to subnormal temperature. Admitted at an age of 3 weeks. Patient had then been subject to shock when nursed. On admission, temp. below 35° C, pale, exuded cold sweat, markedly dehydrated. 750 g below birth weight. On account of similarity to the previous case, and prompt improvement after intravenous electrolyte administration, adrenal cortex insufficiency was suspected. The patient was given NaCl (2.5 g per 24 hours) and Doca (2 mg per 24 hours). After that, steady improvement for 3 months (observation time), apart from two periods, when the therapy was interrupted for control of serum electrolytes. The latter disclosed the following values: *Without therapy* K 25.9 mg%, Na 249 mg%, Cl 340 mg%, HCO₃ 40 vol%, n. p.-N 30 mg%, total protein 5.9 mg%, hematocrit 33 %, WBC 13 600, Eosin. leuk. 6 %. *With NaCl-therapy:* K-23.1, Na-273, Cl-350, HCO₃-36, n. p.-N-41, total protein 5.7, hematocrit 41, WBC 14 200, Eos. 8 %. *With Doca-NaCl therapy:* K-19.2, Na-354, HCO₃-45, n. p.-N-37, total protein 5.2, hematocrit 44, WBC 16 100, Eos. 9.

Glucose tolerance without remark. ECG showed slightly elevated S-T-segment. Increased discharge of 17 ketosteroids (2.7 mg per 24 hours) occurred but genitalia and skeletal age were without remark when 4 months old.

K.-A. Melin and E. Mannheimer: Electrocardiographic investigations after angiocardiology.

As early as about 15 years ago, cerebral angiographies, performed with 35—50 per cent of contrast medium, would, in not a few cases, cause cerebral damage. In later years experimental investigations have shown that contrast solutions, especially when strongly concentrated, will result in considerable injuries.

In angiocardiology, 70 per cent contrast solutions of preparations belonging to the diodrast group are used. In cases of venous angiocardiology, or overlapping of the aorta, as, e.g., in Fallot's tetrad, as well as in thoracic aortography, a not inconsiderable amount of comparatively undiluted contrast medium will pass through the carotid arteries up to the brain. This can be demonstrated in roentgenograms, where the carotid arteries, filled with contrast medium, will be clearly discernible. When patients who have been subject to investigations of this kind are examined electro-encephalographically, changes will be found to remain more than 48 hours after the investigation. In one case the changes remained 5 weeks. In 30 so far examined cases, such changes, after thoracic aortography, have been observed in 50 per cent and, after venous angiocardiology with overlapping aorta, in about 30 per cent.

On the basis of these findings, it is urged that the indications for the use of this investigation method be very strict: that patients with marked electroencephalographic changes not immediately be operated upon; and that a better, less injurious contrast medium be produced.

Sigvard Jorup and Sven-Roland Kjellberg: Studies regarding the colon peristalsis in so-called breast-milk dyspepsia.

Already on their return home from the Maternity Hospital, some breast-fed children have spurting evacuations at every meal, most often when suckling or immediately after finishing. Occasionally, restlessness, flatulence and meteorism will occur. Some of these children suffer from attacks of pain, 10—15 per cent of the children in a normal material have this complex of symptoms. We have roentgenologically studied the intestinal action, chiefly in the colon, in a number of children with so-called breast-milk dyspepsia or, as we call it, hyperperistalsis. 1 1/2—2 minutes after beginning to suck, a marked peristalsis has set in in the colon, with occasional attacks of pain when the colon has strongly con-

tracted. Children with a normal intestinal activity have shown little peristalsis or none at all. No change has been noticed in the small intestine. The symptom complex depends on a lack of balance in the vegetative nervous system in neuro-labile children, which will remain up to the third or fourth month. Our investigations have not been concluded. We have studied the colon peristalsis, particularly during treatment with Skopyl (methyl scopolamini nitras), which has produced good results, rapidly normalizing the intestinal action.

Bengt Jonsson: Distal tubular nephritis in newborns.

During their first days of life, three severely asphyctic newborn infants showed a pronounced oliguria and a uremia with a nonprotein nitrogen increase of 90—127 mg%. One of the children died and, at postmortem, renal changes entirely typical of distal tubular nephritis (lower nephron nephrosis) were disclosed. The two other children improved rapidly after the first week of life. They did not afterwards reveal any signs of renal disease. All three children had marked symptoms of shock, and the consequent disturbance in the renal circulation, in all likelihood, originated the renal damage.

C. G. Bergstrand, B. Hellström and B. Jonsson: Some views on the technique of counting eosinophil cells.

A. Dahlström: Two cases of C virus infection.

Case 1: Girl, 7 years old, had stomach pains without nausea or vomiting. As the stomach troubles abated, there was an acute onset of high temperature (40° C), disappearing after 24 hours, together with a persistent headache and sore throat. On the 12th day of the disease, admitted to the hospital, then disclosing a moderate neck stiffness. The headache gone. Moderate pharyngeal redness. The physical examination otherwise without remark. The cerebro-spinal fluid showed a slight pleocytosis (17 cells) and faint positive protein reaction (Pandy's test: trace). C-virus isolated in samples of feces. C-virus antibodies present in blood samples from the patient.

Case 2: Boy, 4 1/2 years old, who, on return home from a stay in the country in the later part of the summer, for two days complained of pains in his legs. On the 3rd day, he developed a high temperature (40° C) which remained for a few days. Then, entirely free from symptoms and active for about a week. After this, he again began to complain of pains in the legs, especially on the left side. Admitted to the hospital on the 11th day of the disease, then had a faint headache and intense vomiting, the pain in the legs remaining. At the admission, moderate redness in the pharynx and slight reduction of the left patellar reflex. In the

cerebro-spinal fluid no cells, while protein reactions were positive (Pandy's and Nonne's tests positive). Otherwise, the physical examination without remark. C-virus found in feces, antibodies in the serum. Remained at the hospital for 11 days, free from symptoms. After his discharge, he has disclosed no signs of disease.

Meeting, October 13, 1950.

M. d'Avignon and S. Norstedt: On the diagnostic BCG reaction (Ustvedt) (to be published in the Acta Pædiatrica. 1951).

Bo Vahlquist: Iron preparation for intravenous therapy.

Ordinary iron salts, such as ferrous sulphate, have a toxic effect after intravenous administration in doses exceeding 0.15 mg/kg of body weight. This is due to the fact that the iron-carrying capacity of the plasma has been surpassed; hence the iron dialyses out of the vascular system. When in a colloidal, non-dialysable form, iron can be administered in larger amounts. During the past few years, the use of *iron saccharate* has become widespread. Recently, a Swedish preparation of this kind, called *Intrafer*, has been produced. The dosage for adults is given as: 30 mg — 60 mg — 100 mg, etc., that for children as: 10 mg — 30 mg — 60 mg, etc.

Intravenously administered iron is used in roughly 100 per cent for hemoglobin formation. Accordingly, on the basis of the hemoglobin level and the weight of the child, the approximate amount of iron needed for restoring the blood values can be calculated according to the following equation: Body weight in kilograms \times hemoglobin deficit in grams% \times 2.5. To take an example: a child of 9 years of age, with a weight of 30 kg and a hemoglobin value of 8.2 g% instead of the normal 12.8 g%; $30 \times (12.8 - 8.2) \times 2.5 = 345$ mg iron. In hospital patients, successful attempts have been made to administer the total amount of iron by intravenous drip during the course of one day. The response to the iron therapy is evident after three or four days. By then the reticulocytes show a marked increase and the hemoglobin values begin to rise. The time elapsing until a complete cure is obtained depends on the initial hemoglobin values, being as a rule about three to four weeks.

The indications for intravenous iron therapy may be stated as follows:

- 1) In cases where a rapid cure of the anemic condition is essential.
- 2) In patients not tolerating oral iron therapy.
- 3) In order to obtain a stimulating effect of the iron on the bone marrow.

However, pediatricians admit the practical limitations of intravenous iron therapy, though it may prove of value in conditions such as the

following: In anemia of an iron deficiency type due to coeliac disease or ulcerous colitis. It may also be tried in chronic infections, such as rheumatic fever with anemia.

Finally, the author wishes to mention a few experimental observations made in cooperation with Dr. Dickie from Belfast. It appears that part of the iron in the saccharate preparations is strongly bound. With the ordinary serum iron technique acc. to Heilmeyer and Plötner, only about 2/3 of the total iron in the solution will react with the orthophenanthroline. This explains why the rise in serum iron observed 5 minutes after intravenous injections in human beings and animals is materially less than that calculated. Serum iron determinations after the intravenous administration of iron saccharate show a rise which may go far beyond the saturation limit without producing any toxic effects. In rabbits, 10 mg per kilogram of body weight of iron can be tolerated without any side effects. With larger amounts, 80 or even 160 mg/kg of body weight, severe cerebral and pulmonary signs may develop and go on to a fatal issue.

J. Lind and C. Wegelius: Relation of cardiac silhouette to cardiac contraction phase.

In the x-ray diagnosis of the heart in recent years, alongside of estimations of the configuration of the heart and heart volume determinations, increasing significance has been attributed to the cardiac movements. Kymographic and electro-kymographic recordings of the movements of the cardiac outline illustrate this. As regards the prerequisites for estimating the movements of the cardiac outline, as visualized by radiography, the not inconsiderable source of error inherent in the rotary movements of the heart and its displacement as a whole during cardiac activity should not be disregarded. It involves a registration of different, not the same, points in different cardiac and respiratory phases in tangential projection. For this reason, a third alternative was tried to estimate the deviations in the cardiac silhouette, viz. in relation to the cardiac activity as visualized by angiocardiology. The angiocardiology method elaborated at Norrtull's Hospital was employed, with synchronous photography in two planes, a picture speed of 10 per second, and simultaneous ECG recording with exposure markings. This method was combined with a picture technique visualizing in one and the same picture the external cardiac contour as well as, simultaneously in the heart, the angiocardiology manifested cardiac cavities. The ECG taken at the same time allows exact control of the particular cardiac phase exposed in the picture. The results of the examination show that the different cardiac sections may be clearly stated to have, each one separately, a specific evacuation mechanism that is only partly, and in a

varying degree, reflected in the peripheral silhouette movements, inter alia owing to the varying appearance of the individual cavities in the cardiac outline. A continuous angiocardigraphic recording of the dynamically effective process at variations in form and size of the cardiac cavities must, therefore, offer a clear conception of the real nature of cardiac activity. At the same time the deviations in the cardiac silhouette obtain their natural explanation in the light of the dynamic course of the cardiac activity in its entirety.

Michel Alexandre: Neuf cas de primo-infections tuberculeuses après vaccination au B.C.G. ont été rapportés: Vaccination avec ensuite Mantoux positif, et début de la maladie au moins un an après (en moyenne 2 ans, 7 cas sur 9).

La tuberculose a été vérifiée par la radio, l'évolution clinique et soit le contag, l'érythème noueux, la tubage gastrique.

Les symptômes initiaux furent banaux, la tuberculose a été découverte, soit à la suite d'un examen systématique, soit après l'apparition d'un érythème noueux (2 cas sur 9). Les vitesses de sédimentation étaient autour de 30 mm environ. Il n'y avait pas de fièvre à l'entrée, un rare fébricule ensuite dans deux cas. Un seul tubage gastrique fut positif. Dans 8 cas sur 9, la gorge était un peu rouge et il y avait des ganglions superficiels: On trouva du streptocoque hémolytique dans 5 cas sur 9. La radio montrait des images de primo infection droite et gauche. L'évolution fut bonne, durée moyenne du séjour à l'hôpital 45 jours. Il y avait des signes de neurolabilité dans 6 cas sur 9.

Henrik Lichtenstein (in collaboration with George M. Guest and Josef Warkany, Cincinnati): Skeletal abnormalities in the offspring of white rats given protamin zinc insulin during pregnancy.

Sub-shock doses of protamin zinc insulin (Lilly) given daily as a single dose subcutaneously (7 to 8 units) to pregnant albino rats from the second day of pregnancy have significant effects on gestation. Owing to fetal deaths and resorption, the litter size is smaller and the average weight of the fetuses lower. No gross malformations of the skeleton were found, but the skeletons in a considerable number of the fetuses showed incomplete staining. This was interpreted as an incomplete ossification. Irregularities in the shape and staining of the long bones were also observed. In a few fetuses minor deviations in the shape of the ribs were noted. From the data presented no conclusions can be drawn regarding the mechanism of the action of protamin zinc insulin in its effect on fetal gestation.

Meeting, November 11, 1950.

Samuel Levine (New York): **Retrolental Fibroplasia.**

Henry L. Barnett (New York): **The Effect of ACTH on Children with the Nephrotic Syndrome.**

Preben Plum (Köpenhamn): **Hilde Bruch's Fat Children.**

Genevieve Stearns (Iowa City): **Calcium and Vitamin D Requirements during Childhood.**

BOOK REVIEW

Lehrbuch der Pädiatrie. By G. FANCONI and A. WALLGREN, 1st Edition. Benno Schwabe & Co. Verlag, Basel, Schweiz. Price SFr. 62.-.

Medical students from central and northern Europe for many years adhered almost solely to textbooks of pediatrics in the German language. Following World War II textbooks by English or American authors, many of them of outstanding quality, were used increasingly. Once again, however, textbooks in German have made their appearance.

A very interesting newcomer is the textbook of pediatrics edited by Fanconi and Wallgren, which appeared in 1950. A number of pediatricians, mainly from Switzerland, Scandinavia and Holland, have cooperated in this volume. An English edition will appear in the near future.

It is not surprising that the 1st edition still lacks some organization in the presentation of various chapters. Many of them, e.g. those dealing with psychology of the child, with anemias, with acute infectious diseases, with tuberculosis and respiratory diseases, are well adapted for students training; others are, according to the writer's opinion, not quite simple enough. A Scandinavian student will probably find many practical aspects to be neglected in the chapters on childfeeding. Extensive use of small print in many other chapters will probably make him feel the reading somewhat hard.

A few other comments should be made. The prophylactic treatment of the nipples during the last period of pregnancy ought to be mentioned in the chapter on feeding. The same is true for self-demand feeding and the great variations in the amount of milk needed for children of the same age and weight. The prematurity problem has such a general and wide importance that somewhat more space ought to be given it. Hemolytic diseases of the newborn, necessarily including a detailed presentation of isoimmunization against Rh, might preferably be included under "Hemolytic Anemias" rather than under "The Newborn Period". The discussion of diabetes in the general chapter on metabolic disturbances rather than in the chapter on endocrine disorders may be questioned. The same is true for the time-honoured separation, found in most or all German textbooks, of diarrhoeal disorders in infants from gastro-intestinal diseases.

The illustration of the new textbook is unrivalled in its wealth of excellent photographs, many of which are in colour, of first-class repro-

ductions of X-ray pictures and instructive diagrams. An unavoidable draw-back of the high standard in this respect is the comparatively high price of the book.

To all evidence a second edition will have to appear within a short time. It is to be hoped that the material will then be ideally organized. The presentation of all necessary facts and practical hints in the text and of the detailed surveys and differential diagnoses in figures and tables is a good solution and is already adopted in many chapters of the present edition.

It is no overstatement to say that, despite the few technical difficulties relative to arrangement and details, this new textbook of Fanconi and Wallgren in myriad ways reflects the great knowledge and ability of the editors and their contributors.

Bo Vahlquist.

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HENNING MAGNUSSON

in memoriam

The chairman of the Section of Pediatrics and School-Hygiene of the Swedish Medical Society, docent Henning Magnusson died on June 4th. He was 47 years of age. He got his pediatric education under Jundell and Wernstedt at the Norrtull's Hospital, where he later served as head of the outpatient department and later for two years as professor and teacher in pediatrics at the Royal Caroline Medical Institute. In 1944 he was appointed chief of the Sachs' Children's Hospital. He had the opportunity to plan the design of the new hospital, to which he was subsequently appointed chief, and did this in such a way that this hospital has turned out to be one of the most modern and beautiful of children's hospitals in Europe.

He began, during his years as resident at Norrtull's Hospital, to publish his numerous scientific papers, among others his exhausting work on the blood of premature infants. His scientific disposition bloomed after he overtook the responsibility of the Sachs' Hospital, where he drew together a team of young, research-minded co-workers, with whom he collaborated. Among the more important studies that Magnusson has done may be mentioned his poliomyelitis studies, his toxoplasmosis investigations, his production of and tests with BCG-tuberculin, his inspiring experiments to combat nosocomial infections and his clinical trial of amino-acid-hydrolysates in feeding of premature babies. He had the great ability to associate himself with various prominent representatives of the basic medical sciences, especially biochemistry, bacteriology and virology, which in a high degree enriched his production. His scientific publications are characterized by solidity, clarity, and sound judgement.

Personally Magnusson was a modest kind man who quietly went his way, carefully avoiding unnecessary obstacles and situations involving strife and conflict. He was a peaceful and serene man, an uncommonly solid and noble personality. He devoted himself to his patients, was loyal to his colleagues, a gentleman and an honour to the Swedish physicians.

FROM THE PEDIATRIC CLINIC OF THE CAROLINE INSTITUTE AT KRON-
PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.

Precocious Puberty

Clinical Picture and Remote Prognosis

by

HANS-OLOF MOSSBERG, M. D.

The causes of precocious puberty may be classified as 1) Cerebral, 2) Adrenal, 3) Gonadal and 4) Constitutional.

Numerous instances of the various types have been reported but there have been but few isolated communications concerning the remote prognosis, and these commonly after only short periods of observation. The present study offers a short description of the various types of precocious puberty (p. p.), including the clinical picture and the findings of hormone analyses, and also a report of the re-examination of several cases from Kronprinsessan Lovisa's Children's Hospital (K. L. B.), Stockholm, 3 to 14 years after hospitalization. This follow-up has in certain instances shed further light on the ultimate prognosis.

Cerebral precocious puberty

According to the literature the cerebral group of p. p. includes tumours of the pineal body and changes in the hypothalamus (tumour, inflammation, vascular disturbances, hemorrhage, hydrocephalus).

Hyperfunction of the pineal body is no longer considered etiologic to p. p., as no specific endocrine function of this gland has been demonstrable in animal experiments. According to RUSSEL & SACHS (cit. HAIN 1947) tumours of the pineal body produce p. p. either directly (embryonal tumours, teratomas, or mixed tumours) or through pressure on the hypothalamus

and/or its innervation. The report of WEINBERGER & GRANT (1941) suggests that in the cerebral cases the condition is a purely hypothalamic syndrome in which the lesion is localized to the posterior portion of the hypothalamus.

The clinical symptoms in damage to the posterior hypothalamus include a tendency towards low fluid intake, oliguria, tachycardia with absence of fever, and disturbances of behaviour (attacks of frenzy, unrestrained conduct). In expanding lesions signs of increased intracranial pressure often becomes evident.

Due to the abolition of repressing impulses from the posterior hypothalamus to the pituitary this latter produces an excessive amount of gonadotropic hormones. These hormones cause an isosexual p. p. The urine of such patients contains abnormally large amounts of folliculin and androgenic substances.

The treatment in these cases is mainly palliative. Radical surgical intervention is impracticable because of the site of the changes.

According to NOVAK, 1944, cases of the so-called ALBRIGHT's *syndrome* probably belong to this cerebral group of p. p. This syndrome was initially described by ALBRIGHT, HAMPTON & SMITH in 1937. The clinical picture is dominated by general skeletal changes (osteitis fibrosa generalisata with bone cysts) and cutaneous pigmentation. This condition occurs almost exclusively in girls.

Adrenal precocious puberty

The adrenal group comprises cases in which the adrenal cortex is the site of tumour or hyperplasia. The result is an increase in the adrenal cortical function leading to the so-called adreno-genital syndrome.

The clinical picture varies, depending on the sex and on the age of the patient at the onset of disease. If the condition originates in foetal life there arises, in foetuses of either sex, pseudo-hermaphroditism with more or less differentiated external genitals, while the internal genitals are isosexual. If the disease begins in early childhood there results, in boys, isosexual p. p., viz: precocious sexual maturation in the masculine direction, although

with absence of spermatogenesis. In girls there is a heterosexual p. p., viz, a precocious sexual maturation with masculine characteristics (hirsutism, deep voice, acne, boyish build, enlargement of clitoris) (HAIN 1947, BERGMAN 1947). Menstruation or vaginal bleeding is uncommon prior to the age of 11 (REILLY, LISSER & HINMAN 1939).

In the adrenogenital syndrome the excretion of 17-ketosteroids in the urine is markedly raised, which is consistent with the masculine traits of the clinical picture. In some instances, however, there is also observed a rise of the folliculin excretion (GROSS 1940, and others). FRANK (cit. REILLY *et al.* 1939) describe 2 adult females with masculinization, in whom the folliculin excretion was markedly increased. GROSS (1940) referring to the "estrogenic substance" in the adrenogenital syndrome summarizes: "the findings of large amounts of urinary estrogenic substance (in the absence of a positive test for pregnancy) is highly suggestive of a cortical adrenal neoplasm, but negative results do not rule out such a neoplasm." No cases with an elevated folliculin excretion in boys with the adrenogenital syndrome have been described hitherto (Case 1).

Therapy is directed towards the causative agent, the adrenal tumour or hyperplasia, and consists in a more or less radical removal. As the malignant tumours involved metastasize rather late, early operation improves the prognosis. In the case of hyperplasia the indication for operation is not absolute. Thus, according to SECKEL (1946) the result of this operation is unsatisfactory in girls and is considered needless in boys. The risk factor in the operation is shock. It is advisable to treat the patient with cortical adrenal hormone and to exert meticulous control of the blood electrolytes before, during, and after the operation. Solitary instances of successful operation have been reported, for example, by REILLY, 1944. As regards the remote prognosis we have but little knowledge.

Case 1. A. R., male, born 24.3.1939. Case record 801/41.

Case history. No known instance of endocrine disturbance in the family. An elder brother, with slight pubic hair growth at 2 years of age, died at 5 years of age with vomiting and diarrhea.



Fig. 1. Case 1. Boy, aged $2\frac{1}{2}$, with precocious puberty (adrenogenital syndrome), compared with a normal boy of the same age. Note the marked somatic development, the pubic hair growth, and the extreme genital development.

Birth weight 3 600 g. Normal delivery. Moderate eczema of cheeks, wrists, and inner aspects of the elbow joints at 6 months of age.

Completely normal development up to 18 months of age. Had his first tooth at 6 months, walked at 14 months, and talked (isolated words) at 12 months. At 18 months he gradually became larger than other children of the same age. At $1\frac{3}{4}$ years the pubic hair began to appear and the penis increased in size. Absence of onanism. Frequent urination with enuresis. Admission to K. L. B. for study 8.9. 1941 ($2\frac{5}{12}$ years).

Physical examination: On admission he was 105 (+ 13) cm tall and weighed 17.5 (+ 0.1) kg. He was large and sturdy for his age (Fig. 1) and obviously embarrassed by the examination. His musculature was not particularly well developed. His voice was childish. The hair of his scalp was flaxen. There was no demonstrable growth of facial hair. The pubic hair was profuse with dark brown hairs several centimeters in length. Hair was also present on the scrotum. In the axillae and around the nipples there was noted a growth of $\frac{1}{2}$ cm long fine hairs. On the remainder of the body there was no increased hairiness.

External genitals: The penis measured 8 cm in length from the root to the tip of the prepuce, and was flaccid. The prepuce was rather long, and ensheathed the glans, but was easily drawn over this. The testes were approximately the size of dessert almonds and both were palpable in scrotum. *Fundi:* Normal. Internal organs: Absence of pathological findings. *Blood pressure:* 105/70. *Laboratory data:* *Urine:* Analysis for androgenic substances: 9/12: 121 S. U. (spectrophotometric units); 9/25: 50 S. U.; 10/2: 32.6 S. U. (normal max. value for children 10 S. U.). *Glucose tolerance test* (17.5 g glucose orally): high tolerance (fasting level 72 mg %, maximum value 114 mg % after 2 hours, return to resting level after 4 1/2 hours). *Adrenalin tolerance test:* (0.5 mg adrenalin subcutaneously) fasting value 66 mg %, maximum value 170 mg % after 1 hr., return to resting level after >4 hrs). *Calcium:* 12.4 mg % and 11.4 mg %. *Phosphorus:* 3.9 mg % and 4.6 mg %. *Chloride:* 57.5 mmol. *B. M. R.* —4 % and —3 % (according to Krogh). *X-ray:* Skull: Sella turcica "normal in size, absence of suprasellar calcifications." Skeleton: (hand, foot) corresponding to at least 6 years of age. Abdominal scout film: negative findings. *Urography* (intramuscular): Absence of deformities or filling defects of calices or renal pelvis. Negative findings. *Intelligence test:* (according to Binet-Simon) I. Q. 134.

Operation: Exploratory exposure of both adrenal bodies with partial resection of the left adrenal. The right adrenal body had an entirely normal appearance, except that it was possibly rather smaller than might have been expected. The left adrenal body showed quite a different picture: it was nearly twice the size of the right, with a coarsely granular greyish-red surface. Two-thirds of the left adrenal were resected. The kidneys had a normal appearance.

Pathological examination: (Prof. H. Bergstrand). Microscopic preparation: Zona glomerulosa has a normal appearance in the various stains. Zona fasciculata exhibits an extremely marked dilatation of the capillaries which are rather exsanguine. Ponceau-Fuchsin staining reveals that large areas of this layer are fuchsinophil. A number of the most markedly fuchsinophil cells stain red with Mallory's stain. These cells exhibit pyknotic nuclei. Fat stains reveal a normal lipid content.

Course: After discharge from hospital in 1941 the patient has had neither symptoms nor complaints, except that he has grown rapidly and because of his size has felt ill at ease with playmates of his own age. He was admitted to Sachska Barnsjukhuset, Stockholm, in 1945. At this time he was less interested in toys than other children. He was rather stubborn and extremely active. He was fond of discussing various subjects and was interested in books although he did not care to read much. Enuresis had persisted since childhood. There was no masturbation. On examination at the hospital 30.10. 1945 he was 151 (+ 28) cm tall and weighed 37.3 (—3.4) kg. Shoe size 37. External genitals:

penis about equal to that of an adult. Testes approximately the size of a hazel nut, in scrotum. Pubic and axillary hair similar to that at the age of 16 to 17 years. Nipples and areolae of nearly adult type, no hairiness of chest. Blood pressure 150/70. Fundi not remarkable. Neurologic status: not remarkable. I. Q.: 114. Glucose tolerance test: (0.75 g/kg body weight) fasting value 105 mg %, max. value 157 mg % after 45 min., return to resting level after 2 1/2 hours. Urinary androgen excretion: (*Luft*) 50 mg/24 hrs., twice the value of adult males. 17-ketosteroid determination: (*Mattson*) 56 mg/24 hrs. — Urinary sodium and chloride excretion 13.3 % per 700 ml/24 hr sample, corresponding to 9.3 mg NaCl/24 hrs. *Blood*: Phosphorus 5.8 mg %. NaCl 619 mg %. *X-ray*: Sella possibly rather small. Skeleton equal to age of 12—13 years. Abdominal scout film and urography: negative findings.

Follow-up 29.8. 1949. The patient has had acute otitis and morbilli since the examination in 1945. Abrasio was performed in 1947 for speech difficulties (nasalization). There have been isolated episodes of headache over the parietal region. There has been no abdominal pain although the patient occasionally has complained of stabbing pain on the left side, radiating downwards. There has been no difficulty in micturition and no enuresis. There have been no erections, according to the patient himself. He has not been interested in sex. He does not avoid the company of girls, but has boy and girl playmates. He has been slightly feminine in manner. He is fond of helping with the household chores, enjoys the company of adult women, and is always very neatly and carefully dressed. He does very well in school, being one of the best pupils in his class. He is physically and mentally efficient. Children of his own age tease him because of his bodily size and ungainliness, while older children, of his own stature, do not care for his company as he is too childish for them. His situation has been difficult and he has at times been depressed and unhappy over his pronounced development. His disposition is fairly equable, without tantrums or outbreaks of rage. During recent years his contemporary playmates have begun to catch up with him in growth, the difference thus being smoothed out gradually.

At follow-up examination 20.8. 1949 (10 5/12 years) he was 163 (+25) cm tall and his weight was 48.3 (—2.4) kg. He was tall, lanky with a kyphotic chest and poor posture (Fig. 2). Average nutrition. Scars from operation of 1941. He exhibited various acromegalic traits with a rather large chin, nose, ears, hands and feet. Shoe size 38. Sweaty hands and feet. Pitch of voice deep. He was slightly tanned but had no other pigmentation. The skin was soft and smooth. No acne. Thyreoides: Not palpably enlarged. — *Hair distribution*: The hair of the scalp was average in amount and cendré in colour. The eyebrows were markedly developed. The upper lip had a definite growth of hair, whereas that of the chin was negligible. Abundant pubic and axillary hair. The pubic

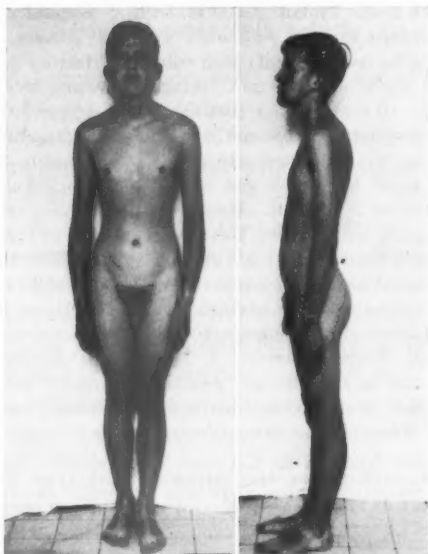


Fig. 2. Case 1. Boy with precocious puberty (adrenogenital syndrome) at follow-up examination at $10\frac{1}{2}$ years of age. Note the tall and slender bodily development, the femininely wide broad pelvis, the triangular distribution of pubic hair, and the rather uncertain facial expression.

hair showed a feminine distribution, triangular with a marked upper margin and insignificant growth towards the umbilicus. The hair growth of arms, legs and scrotum was quite abundant, much as in an adult male. *External genitals*: Penis was 11 cm in length, flaccid, and similar to that of a normal adult male. The prepuce was readily drawn down over glans, on the tip of which the urethra opened out. The testes were palpated, were equal in size (about $2\frac{1}{2} \times 2\frac{1}{2}$ cm) and descended into the scrotum. *Per rectum*: Prostate felt large for the age, but rather smaller than that of an adult. *Heart*: Nothing pathological. *Blood pressure*: 115/75. *Pulse*: 70/min. *Lungs*: Nothing remarkable. — *Abdomen*: No palpable resistance. Liver and spleen not palpable. — *Fundi*: Normal findings. *Psyche*: Rather embarrassed by the examination. Has a gentle, rather yielding manner, conveying a feminine impression. *Laboratory data*: *Urinalysis*: Absence of spermatozoa following prostatic massage. Determination of 17-ketosteroids, 64 mg/24 hrs (normal value 10–15 mg/24 hrs). Folliculin $> 25 < 125$ M. U./24 hrs (normal value

< 25 M. U./24 hrs). Prolan > 400 M. U./litre (normal value 0—20 M. U./litre). *Aschheim-Zondek pregnancy reaction positive*. *Glucose tolerance test*: 1 g/kg body weight) high tolerance (fasting value 69 mg %, max. value 87 mg % after 30 min., return to resting level after 2 hrs). *Blood*: Calcium: 10.6 mg % and 10.3 mg %. Phosphorus: 4.8 mg % and 4.4 mg %. Phosphatase: 108 and 113 units. Potassium: 16.6 mg %. Sodium: 318 mg %. Chlorides: 346 mg %. Cholesterol: 133 mg % and 128 mg %. — *B. M. R.*: ± 0 % and $+ 2$ %. — *X-ray*: Skull: Sella turcica 53 mm² (normal 60.2 \pm 14.9). Absence of destruction or calcifications. — *Skeleton* (hand, foot, elbow): Development equal to that at age 17. — *Abdominal scout film*: Right renal shadow is visualized clearly, the left is partially covered by the stomach. No displacement of the renal shadows or calcifications over the adrenals visualized. *Heart*: Neither shape nor size are pathological. Volume 405 ml = 275 ml/m² surface area. *Intelligence test* (Terman-Merrill): I. Q. 139. His feminine disposition was apparent also at the testing: "gentle and girlishly yielding, anxious to make drawings, etc., neat and attractive." *Urinary output*: 760—850 ml/24 hrs. — *Fluid intake*: 900—950 ml/24 hrs.

This case exemplifies the adrenogenital type of p. p., with the early onset of isosexual p. p. and markedly increased amounts of male sex hormone in the urine. Furthermore the patient exhibits a markedly feminine disposition with a corresponding increase in urinary folliculin excretion. Another noteworthy feature is the high prolactin excretion which also caused a positive pregnancy reaction. The causation of the condition is in all probability to be sought in the adrenal glands, as there is no evidence of cerebral or hypophysial tumour or of true hermaphroditism. On examination of the adrenals in 1941 one was pathological and the microscopic examination showed changes in the zona fasciculata, where the cells in part revealed pyknotic nuclei. This may be suggestive of neoplasm. At the follow-up examination in 1949 the patient exhibited no disturbances of electrolyte balance and the hormonal excretion was unaltered in regard to the 17-ketosteroids. The process seems to be stationary, judging from the examinations. The remote prognosis must be considered questionable, however. Cases of this type in boys are extremely infrequent and it is of great interest that the patient has been observed over such a long period of time.

Gonadal precocious puberty

The gonadal group includes cases in which a tumour or cyst is localized to the ovaries or testes.

The ovarian tumours are of various types: granulosa cell tumours, chorionepitheliomas and arrhenoblastomas (HAIN 1947, CHRISTENSEN 1947).

According to CHRISTENSEN the *granulosa cell tumours* are commonly associated with extremely high urinary folliculin values (65—17 300 M.U./litre urine). The tumour causes an isosexual p. p. with early occurrence of vaginal bleeding. The malignancy is variable, but the tumour is usually fairly benign, for which reason early radical intervention may lead to complete recovery with reversal of the symptoms of p. p. (Case 2).

The *chorionepitheliomas* are considerably less frequent in childhood and only a small number of evident cases have been described. These tumours are very malignant and metastasize early. They give rise to isosexual p. p. with a high gonadotropin excretion (30 000—60 000 M.U.).

The *arrhenoblastomas* have a virilizing effect but do not occur in childhood. According to GROSS the youngest patient reported was 15 years old.

Tumours of the testis are rare. They are mainly in the interstitial cells and induce an isosexual p. p. with increased 17-ketosteroid excretion (BERGMAN 1947). Other testicular tumours may produce a high gonadotropin value (HAIN 1947). As to the prognosis we have but little knowledge. (Case 3.)

Case 2. M. Ö., girl, born 15.9.1931. Record No. 767/35. (MANNHEIMER's case: J. Pediat. 12: 350—356, 1938.)

Case report. (For further detail see MANNHEIMER's paper.) No history of sexual abnormality in the family. The mother has always been healthy; her menarche occurred at the age of 12 years.

Patient's birth weight 3 200 g. Breast-fed. Development apparently normal during the first 3 years of life. In December 1934 a vaginal discharge appeared. In September 1935 the patient had bleeding from the vulva for 2 days. In October 1935 there was a similar bleeding. In the beginning of 1935 there was a pronounced increase of growth and the breasts developed to a size distinctly larger than in children of

comparable age. There was no hirsutism or sexual abnormality. Mentally, the patient resembled other children.

Physical examination: On admission to K. L. B. 28.10. 1935 the patient was 117 (+14) cm tall and weighed 26.7 (+5.5) kg. She was in good general condition. Her build was in proportion. Her general appearance was comparable with that of a girl in late puberty, with large breasts, areolae and nipples, and with early axillary and pubic hair growth. She was embarrassed by the examination. Mentally, she seemed considerably older than her chronologic age. "Womanly" facial expression. Heart and lungs physiologically normal. Blood pressure 120/80. Abdomen: No resistance palpable. Neurological examination: Nothing pathological. Fundi normal. *External genitals:* Labia minora and majora rather larger than usual. Clitoris of normal size. *Rectal examination:* Dextrolaterally a tumour the size of a goose-egg is palpated, well defined from the firmer and smaller anteflexed uterus, which is large in relation to her age.

Laboratory data: *Urine:* Urinalysis for prolan: negative. Aschheim-Zondek's pregnancy reaction: negative. Prolan test on mouse according to Zondek < 9 M. U. prolan/litre urine. *B. M. R.:* + 22 % and + 15.5 % (acc. to Krogh). — Glucose tolerance test: normal findings. — *Intelligence test:* (Binet-Simon) I. Q. 132. — *X-ray:* Skull, abdominal scout film and urography: negative findings. Skeleton: (hand, foot) corresponding to at least 6 1/2 years, more probably close to 9 years.

Operation: 4.11. 1935 at the Surgical Department of K. L. B. Extirpation of a right ovarian tumour the size of a mandarin orange with a fallopian tube the width of a pencil. The opposite ovary and tube and the uterus seemed to have a normal configuration but showed a distinct increase in size in relation to the age of the patient. The post-operative course was uncomplicated.

Pathological examination: The right ovary was transformed into a tumour the size of a mandarin orange: it measured 7 cm in length and was sheathed by an unperforated capsule. The tumour was a polycystic granulosa cell tumour of typical appearance (Prof. F. Henschen). Implantation of 0.1 g of tumour tissue into immature mice showed, by the resultant vaginal changes, that it contained a certain amount of folliculin.

Course: The patient was followed by MANNHEIMER up to 13 months post-operatively. She has since been examined on repeated occasions at the hospital, the last time in January 1942. Development up to this date was as follows:

During the first years after the operation the patient's manner became gradually more and more childish, the "womanly" facial expression and the shyness disappeared, her frame became more childish and the feminine contour less accentuated. The pubic and axillary hair dis-

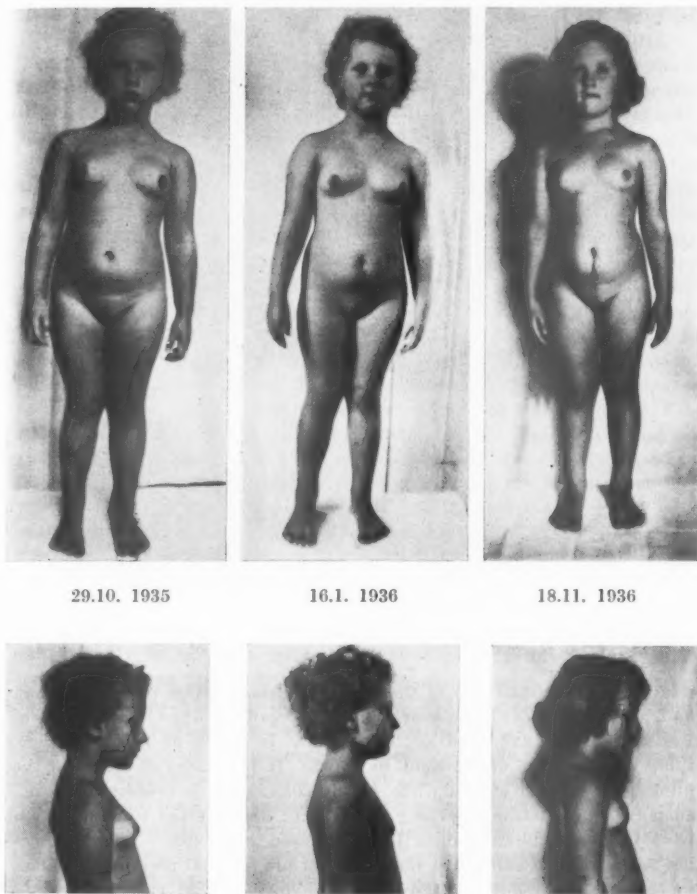


Fig. 3. Case 2. Girl, aged $2\frac{1}{2}$, with precocious puberty (granulosa cell tumour) before and after operation. Note the change to a more childish facial expression after the procedure.

appeared (Fig. 3). The increase in height during the year following operation was only 5 cm as against approximately 7 cm normal for the age. The roentgenological skeletal development was at a standstill. There was no recurrence of uterine bleeding. During the following years there

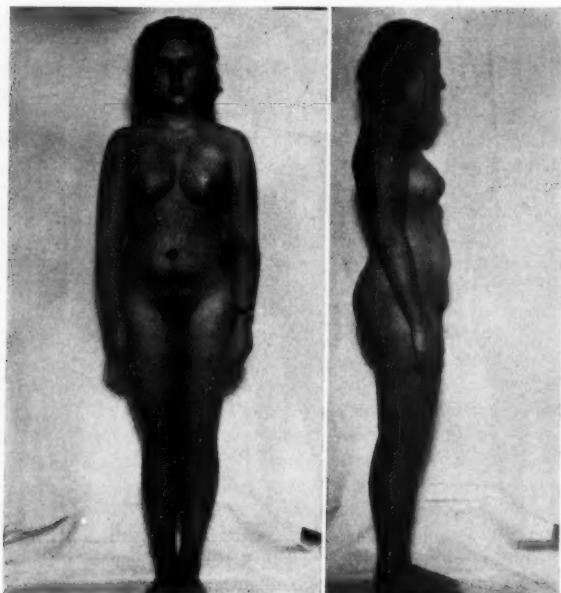


Fig. 4. Case 2. Girl with precocious puberty (operated granulosa cell tumour) at 10 $\frac{2}{11}$ years. Normal rather plump girl in puberty. Looks older than her age.

was a gradual diminution of the excess in height which the patient had had, as compared with the average child, according to the height tables of BROMAN, DAHLBERG, and LICHTENSTEIN. In 1940, at 9 years of age, there was again an acceleration in growth. In December of that year the pubic hair growth started (Fig. 4) and 20.4. 1941, a menstruation occurred. Examination disclosed no signs of any uterine tumour. Analyses for hormone substance (LUFT) showed Folliculin < 20 M. U./24 hrs and androgen substance 43.5. S. U./24 hrs (normal prepuberal values for girls). The roentgenological skeletal development corresponded to about 12 years of age, which was consistent with the somatic development of the patient. She was considered to have reached and passed through an early normal puberty. A check-up 6 months later (Jan. 1942) showed that this conclusion seemed to be correct. The patient had menstruated every month in the meantime. Internal examination revealed nothing pathological. Hormone analysis: (MATTSON): Prolan < 40 M. U./litre; Folliculin < 20 M. U./litre. Reports of her further development are lacking in the hospital record.

Follow-up 8.9. 1949: In 1947, the patient had chicken-pox and mumps. She has had eczema of the armpits every spring and fall since 1945. — The periods have been regular at 28 days interval, and of 5 days duration. In 1942—1944 the bleeding was profuse, but became rather less in the following years; at present it is profuse for the first two days only. Last menses prior to the follow-up examination, 28.8. 1949. There is always a certain amount of discharge, at times a slight stain on the clothes. The discharge increases prior to the period. — Acuity of vision good, but there is fatigability on work at close range (sewing), so the patient uses working glasses. Hearing good. Headache occurs very rarely, then being localized to the forehead without lateralization. She drinks 1 to 5 glasses ($\approx 1\frac{1}{2}$ dl) of fluids between meals daily. Urine output normal. There is abundant perspiration, especially of the axillae. She has always been obese and gains steadily in weight. She is able to lose weight without undue effort. Owing to her present occupation, sewing, she is sedentary but takes a walk occasionally and participates in physical exercise at school. She is capable at her school tasks, definitely above the average. — She is usually rather isolated and has no girl friend. She believes this is due to the fact that she became used to isolation in her early years of school life when school mates of her own age were too childish for her. She has had a boy friend for the last 2 or 3 years. She is not as yet engaged. She becomes very upset if anything outside the usual daily routine occurs, although she herself on many occasions realizes how unreasonable this is.

At *follow-up examination 8.9. 1950*, the patient was 156 $\frac{1}{2}$ ($-8\frac{1}{2}$) cm tall and weighed 77.7 (+29.0) kg. She was diffusely obese especially on thighs, breasts, upper arms and abdomen (Fig. 5). Sturdy build. Her manner was markedly feminine, pleasant, candid, and attractive. She was rather nervous, but intelligent and sensible. Her questions were typically feminine, as "whether she can have children"; "Whether it is worth while, from the cosmetic viewpoint, to undergo a plastic operation of the breasts". — The skin was soft and pliant, not especially moist. There was no eczema of armpits, nor were there striae or acne. Thyroids: Not palpably enlarged. The breasts were large and full, with considerable masses of fat. The glandular tissue appeared normal. *Hair growth:* Hair of scalp light, curly, soft. No hirsutism of the face. The eyebrows not especially conspicuous. The pubic and axillary hair was dark and profuse, developed as in an adult woman. The pubic hair formed a triangle with a rather sharply defined upper margin. — *Heart:* Normal in size. Tones pure, rhythmic. Acc. A₂. *Blood pressure:* 150/80. — *Lungs:* Nothing remarkable. — *Abdomen:* Operative scar in the mid-line below umbilicus. Abdominal palpation is difficult owing to the abundant fat. No pathological resistance palpable. Liver and spleen not palpable. — *Per rectum:* Uterus palpated, anteфлекed, as large as that of an adult

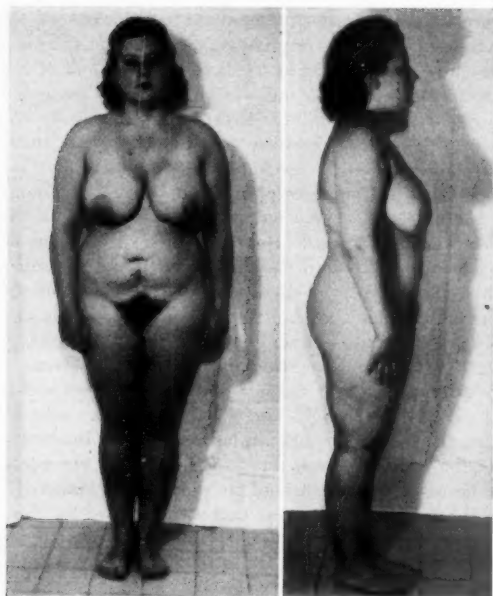


Fig. 5. Case 2. Girl with precocious puberty (operated granulosa cell tumour) at follow-up examination at nearly 18 years of age. Note the entirely normal development of pubic hair growth and of the breasts. Obese. Appearance corresponding to that of a 25-year-old.

woman. No tenderness or resistance on either side of uterus. *External genitals*: Both labia minora and majora are developed as in an adult woman. Clitoris is not enlarged. — Reflexes brisk but not pathological. *Laboratory data*: *Urine*: Analysis for folliculin $> 25 < 125$ M. U./24 hrs. Prolan < 40 M. U./litre. Pregnancy reaction negative. 17-ketosteroids 35 mg/24 hrs. — *Blood*: Potassium: 17.8 mg %. Sodium: 351 mg %. Chlorides: 352 mg %. Cholesterol: 271 mg %. *B. M. R.* $+ 13$ %. — *X-ray*: Skull: Sella turcica 93 mm² (normal 84.2 ± 35.0 mm²). No bone destruction. Skeleton (elbow, hand, foot). All centres of ossification developed and synostosis terminated with union of the epiphyseal lines of junction.

This patient presents a typical example of gonadal p. p. in which the causative agent was a granulosa cell ovarian tumour. Early operation was carried out and the tumour removed in toto

before it had had time to break through its capsule and give rise to metastases. Check-ups of the patient at the out-patient department of this hospital during the years after the operation showed that the rate of increase of growth was checked until the onset of a rather early puberty, and that the development of the patient was normal in all respects, apart from the development of obesity. Follow-up examination 14 years post-operatively showed that the patient was completely healthy, with regular menstrual periods and with absence of signs of metastases. The case is a good illustration of the experiences reported in the literature, stressing the importance of early diagnosis and radical operation, in achieving successful results and a favourable remote prognosis.

Case 3. U. A., boy, born 27.5.1943. Record No. 528/46. (SANDBLOM's case: *Acta Endocrinol.* 1; 107—120, 1948.)

Case history: (For further detail see SANDBLOM's paper). No known endocrine disturbance in the family. Birth weight 3 700 g. Development normal up to the autumn of 1945. At this period, at 2 3/12 years of age, he began to increase abnormally in weight and height. His features became coarse and his skin seborrhoeic. Simultaneously the pitch of his voice began to change. At 2 8/12 years of age it was noted that the external genitals were abnormally large. Coincidentally he became sexually sensitive and had numerous erections. Two months later the pubic hair growth started. He became difficult, ill tempered and irritable. He was interested no longer in playing with other children.

Physical examination: On admission to K. L. B. 6.5. 1946 (2 11/12 years of age) the boy was 108 (+11) cm tall and weighed 21.7 (+3.6) kg. His bodily development was far ahead of his age. (Fig. 6.) His complexion was pale; his lips thick. There were no signs of acromegaly. The facial skin was moist and seborrhoeic. The voice was of a coarse pitch and broke repeatedly. The musculature was markedly developed and firm. — Beginning pubic hair growth. No hairiness of axillae or chest. *External genitals:* Penis was 6 cm when flaccid. The left testis was nearly the size of a plum, the right being barely half this size. Both testes were palpated in the scrotum. — Fundi and blood pressure: No statements. *Laboratory data:* *Urine:* Determination of 17-ketosteroids: (Mattson) 16/5: 23 mg/24 hrs; 3/6: 23 mg/24 hrs; (=normal values for adult male; normal values for patient's age, 2 mg/24 hrs). — *Glucose tolerance test:* Normal tolerance (fasting value 120 mg %, max. value 170 mg % after 30 min., return to resting level in 2 1/2 hrs). *Blood:* Potassium: 27.6 mg % (normal 17—23 mg %). Sodium: 248 mg % (normal 280—

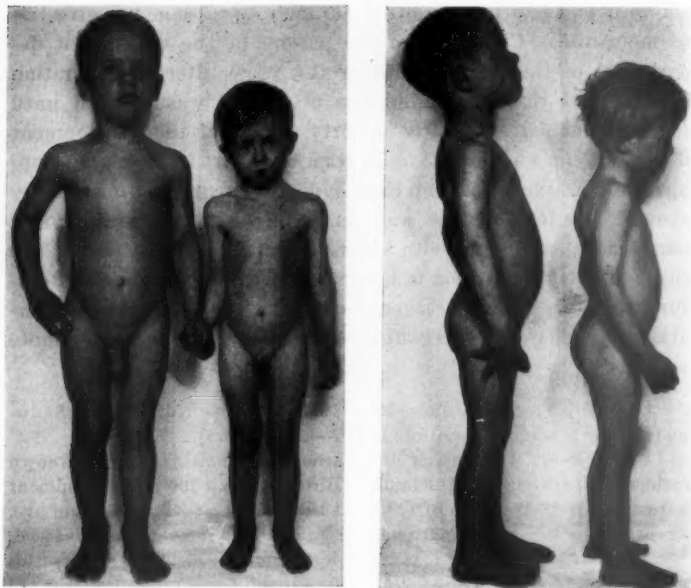


Fig. 6. Case 3. Boy, aged $2\frac{11}{12}$, with precocious puberty (tumour of the testis) compared with a normal boy his own age. Note the pronounced somatic and genital development and the masculine expression and manner. Slight pubic hair growth.

360 mg %). Cholesterol: 150 mg % (normal value 125—225 mg %). S. R.: 15 mm. *X-ray*: Skull: Sella turcica 33 mm² (normal 48 mm²). No destruction. — Skeleton (hand, foot) corresponding to 6—7 years of age. — Abdominal scout film: negative findings. — Urography (intravenous): Absence of deformities of calices or renal pelvis. Negative findings. Intelligence test (Terman-Merrill) I. Q. 111.

The endocrinologist consulted suspected an adrenal tumour, and the patient was accordingly referred to the surgical department for operation.

Operation: (Sandblom) Exploratory exposure of both adrenals with resection of the left adrenal gland. The right adrenal was macroscopically entirely normal. The left was firmer and revealed a dark induration the size of a pea. Before, during and following operation the patient received anti-shock treatment with D. O. C. A., saline, and fluid administration. The post-operative course was uncomplicated.

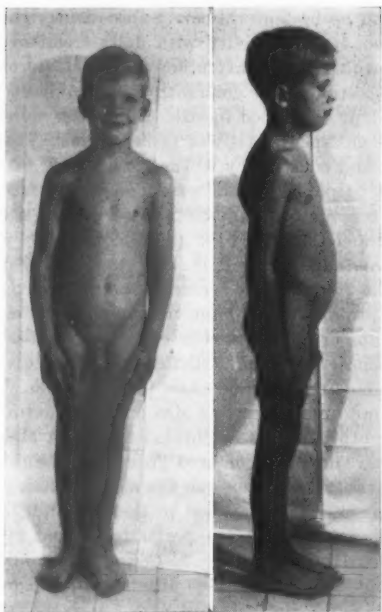


Fig. 7. Case 3. Case of precocious puberty (operated tumour of the testis) at follow-up examination at $6\frac{4}{12}$ years of age. Note the more childish bodily development and the boyish facial expression. Genital development still excessive. Pubic hair growth lacking.

Pathologic examination: (Prof. H. Bergstrand). Three specimens of the adrenal were examined. One of these showed the general architecture of the adrenal. — In the other specimens the architecture was deranged and in a large area of the cortex the capillaries were widened and the parenchyma reduced. Within this area the parenchymal cells took more Ponceau-Fuchsin stain than did the surroundings. Also in the third specimen, which was fixed in chrome, there were heterotopic cortical islands. Staining by Sudan III and osmic acid revealed but little stainable lipoid content of the cells in the glomerular zone. The heterotopic islands of parenchyma aforementioned resembled the glomerular zone in this respect. — *Diagnosis:* Adrenal malformation and circulatory disturbances.

Course: During the 5 months following operation the child gained 10 cm in height and 4 kg in weight (to 118 cm, and 26.2 kg). Immediately

after the operation he became calmer. Subsequently there was a reversion with increased sexual activity with daily erections and sexual advances to adult women. The excretion of 17-ketosteroids increased to 64 mg/24 hrs. Excretion of the gonadotropic hormones remained normal. Penis and pubic hair developed in size. The testes were unchanged except that the left enlarged testis was rather firmer. The prostate gland was equal in size and consistency to that of a young man. The seminal vesicles were not palpable. There was acne of the face. (Fig. 7.)

A left-sided tumour of the testis was suspected, and the *left* testis was therefore removed 16.12. 1946. (Sandblom.)

Pathologic examination: (Prof. H. Bergstrand) "A round tumour, the size of a plum, was found in the centre of the testis, separated by a connective tissue capsule. It was built similarly to the endocrine glands, consisting of groups of epithelial cells resembling follicles, separated by a network of capillaries. The epithelial cells were large, due to abundant cytoplasm, irregular in shape and close to each other. The nuclei were large, mostly round and of varying size and chromatin content. Some were vacuolated, others richer in chromatin. With Mallory stain some of the cells showed small red-coloured granules. Staining by Sudan III and osmic acid was negative, as was the melanin stain of Masson. The adjacent testicular tissue was pushed to the side and did not show any signs of spermatogenesis — it was perfectly normal in appearance. — *Diagnosis:* Interstitial cell tumour." *Course:* SANDBLOM's publication follows the patient up to 12 months after the second operation. Up to 7.12. 1947, he gained 9 cm in height and 1.8 kg in weight (to 127 cm and 28.0 kg, respectively). He became more childish. Although still deep, the pitch of voice was higher. The pubic hair disappeared. Penis was 7 cm in length and 8 cm in circumference. Glans was smaller than one year earlier. The right testis was somewhat larger. The prostate gland had diminished in size and was barely palpable. Blood potassium 17.2 mg %. — *17-ketosteroid determination:* 17 mg/24 hrs.

Since December, 1947, the patient has been followed at the outpatient department. In June, 1948, the urinary 17-ketosteroids were 18 mg/24 hrs and blood potassium was 17.2 mg %. — In April, 1949, the patient, according to a telephone report, was healthy, and was to begin school one year ahead of time, in the fall of 1949.

Follow-up 11.10. 1949: Since December, 1947, the patient has been completely healthy, with the exception of occasional respiratory infections. The general bodily development has been at a standstill and since May, 1949, he has grown only 1 cm. His bodily strength is still disproportionate, but has not increased during the last 2 years. His proportions are more childish. His psyche is advanced in comparison with that of children of corresponding age. No erections have been observed. There is no sign of sexual preoccupation.

At follow-up examination 11.10. 1949, he was 137 (+ 18) cm tall, and weighed 28.0 (—2.9) kg. His build was sturdy with proportionate limbs. (Fig. 7.) The musculature was not especially pronounced and he was well nourished. His manner was childish, corresponding to or slightly ahead of his age. His voice was hoarse and low. Thyreoidea was not palpably enlarged. Absence of axillary and pubic hair. Penis was 6 cm in length and flaccid. Testis, rather larger than a bean, is palpated in scrotum. Heart: Normal configuration. No murmur. Lungs: Nothing pathological noted. *Abdomen*: No palpable resistances. Operatory scar satisfactorily healed. — *Per rectum*: Nothing pathological palpated. *Laboratory data*: *Urine*: Analysis for 17-ketosteroids 14 mg/24 hrs. Folliculin < 25 M. U./24 hrs. Prolan < 40 M. U./litre. *Blood*: Potassium: 34 mg %. — Sodium: 336 mg %. Chlorides: 297 mg %. Cholesterol: 128 mg %. — *X-ray*: Skull: Sella turcica: 64 mm² (normal value 54.4 mm²). Skeleton (elbow, hand, foot): corresponding to 9—10 years of age.

This case is an example of a tumour of the testis with isosexual p. p. in which radical operation removes the causative agent of the precocious sexual development and affords a partial reversal to a condition more normal for the age. In the present case the reversal was most pronounced in regard to the psychic pattern of behaviour and the sexual activity. Analysis of the urinary 17-ketosteroids at follow-up examination, 3 years post-operatively, showed nearly normal values, which indicates that hormone producing tumour tissue is not left behind and that the primary tumour has not metastasized. This gives rise to the assumption that the future prognosis is favourable.

Constitutional precocious puberty

The constitutional group is by far the greatest and comprises cases of isosexual p. p. in both sexes, the children being entirely healthy in other respects. Sexual maturation and somatic development take place in the same manner as in the average child but at an abnormally early age. In distinction to the conditions in the granulosa cell tumours these girls ovulate and may also become pregnant (NOVAK 1944). Later in life they are completely healthy and a case with normal menopause at 52 years of age has been described by HALLER (cit. LENZ 1913).

In these children hormone analyses show a gonadotropin excretion which normally is not present until after puberty. The 17-ketosteroids are excreted in amounts exceeding the average for the age of the patient, but lower than the values found in adrenal cortical hyperplasia or tumour. The folliculin excretion is also higher than is normal for the age.

These features indicate that the condition merely is the unduly early onset of a physiological process. The cause of this is entirely obscure. NOVAK (1944) assumes a chromosomal or genetic origin and therefore terms these cases "constitutional".

It is of extreme importance to distinguish these cases from the pathological types of precocious puberty by means of careful examinations with all the diagnostic aids available, including hormone analyses.

Case 4. B. J., girl, born 21.3.1929. Record No. 108/39.

Case history. Birth weight 2 800 g. Development during the first years of life entirely normal. Walked at 18 months; talked at 18 months. Has always been fat. At 7 years of age her development became accelerated, in comparison with that of children her own age. She became "sturdy" and breast development and pubic hair growth started. Menarche at 8 years of age (Jan. 1938); since that time she has had regular menses every month, with a duration of one week. She became more sensitive and cried on slight occasion. She had tantrums, stamped, screamed and beat the walls. Admitted to K. L. B. for study.

Physical examination: On admission to K. L. B. 3.2.1939, the patient was 147 (+9.5) cm tall and weighed 53.5 (+15.2) kg. She was in good general condition and well nourished. Somatic development was about equal to that of the age of puberty with breast development and pubic hair growth. Axillary hair was lacking. — *External genitals:* Corresponding to those of a girl of 14–15 years, and "normally developed". Clitoris not enlarged. Considerable fluor albus. — *Per rectum:* Uterus about the size of a plum. Adnexae not remarkable. No tumour felt.

Laboratory data: *Urine:* Analysis for folliculin > 20 M. U. < 110 M. U./litre (normal values: adult 20–110, 10-year-old girl 5–10 M. U./litre); Prolan < 40 M. U./litre; 17-ketosteroids: not determined. *B. M. R.* —9% and —13% (according to Krogh). *Intelligence test:* (Terman) I. Q. 92. Cooperative and ambitious at the testing. Rather shy. Equivocal results. Lacks abstract concepts but has a good memory. — *W. R.* negative. *X-ray:* Skull: Small sella turcica, about 6 × 8 mm. Skeleton: equal to at least 11–12 years of age. Urography: Negative findings.

Follow-up 7.10. 1949: Since hospitalization in 1939 the patient has been healthy with the exception of an acute pyelocystitis in 1943 and various diffuse nervous stomach complaints in 1949. Menstruation has been regular every 20th day with a duration of 5 or 6 days. She is quiet and reserved. She has no friends. She is periodically subject to depression and cries for no reason.

At follow-up examination 7.10. 1949 she was 154 (—12) cm tall and weighed 57.4 (+13.2) kg. Date of latest menses 25.6. 1949; she was pregnant. She was indolent and backward. The skin was rather dry. The facial traits were coarse. The pubic hair growth was abundant with a sharply defined upper horizontal margin. The axillary hair was profuse. The breasts were well developed. — Heart: Nothing pathological.

Laboratory data: Hormone analyses not performed. Intelligence test: I. Q. 83. ECG: not remarkable. B. M. R. + 3 %.

The present case is an instance of constitutional p. p. The early puberty of the patient with menarche at 8 years of age (normal age for Swedish girls 14 years, according to LENNÉR), and the absence of any signs of clinically demonstrable tumour substantiates the diagnosis. This case is not particularly remarkable from the clinical viewpoint, but is included because it illustrates the fact that these patients do not deviate from normal in one of the most remarkable functions of the body: pregnancy. The remote prognosis is favourable.

The *social status* of children with precocious puberty is a problem of major importance. Their early sexual and somatic development is not counterbalanced by an equally early mental development. Nevertheless, they often possess a mental development ahead of their chronologic age, although far from corresponding to their somatic age. Mentally, some of these children are aggressive and sexually active, factors which may lead them into situations with which they are unable to cope. Others, again, are shy and timid and thus have better possibilities of passing through the period of adolescence without serious conflicts. The premature somatic development often causes an attitude of inferiority and abnormality in relation to other children. It is therefore of great importance to enlighten their parents as to the true nature of the condition, to advise them to show these children the utmost consideration and understanding, and to

protect them from sexual advances in order to prevent pregnancy. With the passage of time the divergencies will be adjusted and in the cases that attain adulthood the abnormal psychic, somatic and social conditions will have disappeared.

This article was finished in Swedish in March 1950. During the translation LAWSON WILKINS' Monograph of Endocrine Disorders in Childhood and Adolescence was published (Charles C. Thomas, 1st Edition, 1950).

Summary

Various types of precocious puberty (p. p.) are discussed and a number are illustrated by cases treated at Kronprinsessan Lovisa's Children's Hospital in Stockholm. These cases have been followed from 3 to 14 years after hospitalization, thus throwing light on the remote prognosis. The following cases of p. p. are described: a boy with adrenal hyperplasia-(tumour?) in which there was present an abnormal hormone production with a positive pregnancy reaction; a boy with a tumour of the testis; a girl with granulosa cell tumour; and a girl with constitutional p. p. Finally, the mental and social problems of these children are discussed.

H.-O. MOSSBERG: *Puberté précoce. Clinique et Pronostic éloigné.*

Des types variés de puberté précoce (P. P.) sont discutés et un certain nombre d'entre eux sont illustrés par des cas, traités à l'Hôpital pour enfants de Kronprinsessan Lovisa de Stockholm. Ces cas ont été suivis entre 3 et 14 ans après l'hospitalisation, aussi certains d'entre eux éclaircissent le pronostic lointain de ces enfants. Les cas suivants de P. P. sont décrits: un garçon avec une hyperplasie des surrénales (tumeur?) dans laquelle il y avait une production anormalement forte d'hormone, avec, en outre, une réaction de grossesse positive; un autre garçon avec une tumeur des testicules; une fille avec une tumeur à cellules granuleuses; et une autre fille enfin avec une P. P. constitutionnelle. Finalement on discute le problème mental et le problème social de ces enfants.

H.-O. MOSSBERG: *Pubertas praecox. Klinik und Spätprognose.*

Es werden verschiedene Arten von Pubertas praecox (P. p.) besprochen und einige werden anhand von Fällen, die im Kronprinzessin Lovisa-Kinderspital behandelt wurden, erläutert. Die Fälle wurden 3—14 Jahre nach der Krankenhausaufnahme verfolgt und einige Fälle be-

leuchten die Spätprognose für diese Kinder. Es werden folgende Fälle von P. p. beschrieben: Ein Knabe mit Nebennierenhyperplasie(-tumor?) mit Vorliegen einer äusserst abnormen Hormonproduktion und u.a. einer positiven Schwangerschaftsreaktion (!); ein Knabe mit einem Hodentumor; ein Mädchen mit einem Granulosazellentumor; ein Mädchen mit konstitutioneller P. p. Abschliessend werden die mentalen und sozialen Probleme dieser Kinder diskutiert.

H.-O. MOSSBERG: *La Pubertad Precoz: La prognosis remota y clinica.*

Aqui se trata de la pubertad precoz de los cuales algunos son ilustrados por casos que fueron tratados en el hospital de niños de "Kronprinsessan Lovisa" en Estockholmo. Los casos fueron observados desde 3 hasta 14 años despues de la hospitalización, esto por lo tanto aclaraba un poco la prognosis remota para estos niños. Los casos siguientes de la pubertad precoz son descritas: Un niño con hiperplasia adrenal (un tumor?), en lo cual habia una producción hormonal sumamente abnormal, con, inter alia, una reacción positiva de preñez; un niño con un tumor testicular; una niña con un tumor de celulas granulosas; y una niña con pubertad precoz constitutional. Luego se trata de los problemas psiquicos y sociales de estos niños.

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Nutritional Deficiencies, Diseases and Poor Social Conditions During Pregnancy as the Cause of Neonatal Mortality and Illness During the First Year of Life¹

by

CURT GYLLENSWÄRD

The present trend in social welfare aims at creating greater security for the largest possible number. The creation of the greatest possible security for those without whom a nation would have no future — that is, expectant mothers, those who have recently given birth, and children — should be one of the most important tasks for society.

During recent decades the mortality rate in the first year of life has decreased in the western hemisphere to an extent and to a level that would earlier have been regarded as inconceivable. In some countries — Sweden, for example — it has fallen to approximately 2.5 per cent and in a few of its larger cities to below 2 per cent. It was earlier considered that 3 per cent was the lowest possible figure. This was the mortality rate at that time in many families of the nobility and it was therefore assumed that better conditions than were already available for such infants could scarcely be anticipated in the general population. This supposition has, however, subsequently proved to be false. In actual fact, investigations have shown the infant mortality in some very well situated social groups nowadays to be as low as 0.8 per cent.

¹ Paper read at the Sixth International Pediatric Congress, Zurich, July 1950.

A remarkable feature is that this decrease applies only to the mortality rate subsequent to the first weeks of life. That during the very first weeks — *i.e.*, neonatal mortality — has remained on the same level or has fallen only inappreciably. It has even risen during some periods. This is to a great extent the case with regard to stillbirths as well. It is therefore evident that factors connected with or influencing pregnancy, childbirth or the puerperium are at present of greatest interest when considering measures to reduce infant mortality and disease.

The definition of the neonatal period and, hence, of neonatal mortality is not uniform. The first month of extrauterine life was earlier considered as the neonatal period and this is still the case in many countries. However, in countries with a low mortality rate, the mortality is very low during the last three weeks of the first month of extrauterine life whereas it is still high during the first week of this period.

The greater the decrease in infant mortality, the greater will be the relative predominance of deaths during the first week of life. From this point of view, the borderline between the neonatal period and the remainder of the first year of infancy is between the first and second week of life rather than between the first and second month. When an attempt is made to ascertain the causes of neonatal mortality, it is important to rule out periods in which those factors influencing it have already ceased to take effect. Thus, there appear to be very strong indications that the neonatal period should be considered to embrace only the first seven days of extrauterine life. In many countries with a low infant mortality rate — for example, Sweden — pediatricians therefore regard the first week of life only as the neonatal period and only deaths occurring during this time as neonatal mortality (WALLGREN, GYLLENSWÄRD).

Particular attention has been focused on nutrition, illness and poor social conditions during pregnancy among those factors that must be taken into consideration when considering measures to reduce infant mortality and disease. These factors are susceptible to improvement, since they can be dealt with not only by means of medical treatment but by social measures as well.

For example, it has been shown that mothers in the lower social strata give birth to premature infants considerably more often than those better situated. Because up to 50 per cent of neonatal deaths affect premature infants, it is obvious that if the reasons for the high incidence of prematurity could be ascertained a possibility would be afforded of decreasing it. Thus a step would have been taken in the right direction to diminish neonatal mortality. This is emphasized by the fact that the average birth weight is lower for infants in lower social groups than in those better situated (GYLLENSWÄRD). It may be assumed that an excessively low weight at birth is an expression of decreased resistance. By raising the birth weight not only of premature infants but also of those who have, on the average, too low a weight, a favourable effect on illnesses in general during infancy could be anticipated.

We are also aware that the rate of stillbirths, neonatal mortality and infant mortality is higher among those born out of wedlock than within it. It is therefore of prime importance to ascertain those factors that give rise to a poorer prognosis for the infant born out of wedlock and at the same time the extent to which they can be counteracted. It is very probable that malnutrition, disease and poor social conditions during pregnancy can play a rôle (BAIRD, GYLLENSWÄRD). The estimation of their actual effect as a causal factor in neonatal mortality and diseases of infancy is, however, one of the most difficult problems in medicine. The causes of such occurrences are so closely interwoven that it is, as a rule, impossible to differentiate between them.

A few examples can illustrate the foregoing statement. It is a well known fact — almost an axiom — that poor social conditions are commonly accompanied by quantitative or qualitative dietary deficiencies. Certain illnesses in pregnant women are considerably more common if the social conditions — and thus the hygienic as well — are poor. This applies, for example, to syphilis which has long been accorded considerable significance in this connection. It has been described as a curse on the human race. There are, however, other illnesses in which social conditions appear to play no rôle, but which may in fact have a marked

and early effect. German measles is such a disease (GREGG). It is known that its occurrence in a pregnant woman may have a detrimental effect on her foetus. This is of particular interest, since it shows that it is possible for a long-lasting effect — which is neither constitutional nor hereditary in nature — to be exerted on the foetus. The question then arises as to which other diseases fall into the same category and whether nutritional deficiencies and poor social conditions can also have such an effect.

Before considering the matter further it must be pointed out that no definite borderlines can be drawn between spontaneous abortion, prematurity, stillbirth, neonatal mortality and infant mortality. All may be links in the same chain. A causal factor which has a sufficiently early effect may give rise to abortion. If it comes into effect later it may result in prematurity or stillbirth and predispose towards neonatal mortality by retarding development and thus decreasing resistance.

If this successive effect is borne in mind it may permit some check on the accuracy of observations made, as is shown by the following example. An increased incidence of premature births may be found in a certain series and ascribed to a certain factor. If, however, there is not at the same time a relative increase in the number of infants with a particularly low birth weight — although not so low as to constitute prematurity — in the same series, this is a strong indication that the interpretation or observation is incorrect.

It is of less practical interest here to discuss the borderlines between abortion and premature birth. Foetuses concerning which doubts may arise as to whether they should be considered as abortions or as premature are relatively few. With regard to the borderline between premature and full-term infants it need only be noted that, from a paediatric aspect, infants with a birth weight below 2 500 grams should be considered as premature (YLPPÖ).

Nutritional deficiencies have recently been accorded particular attention among the possible causes of foetal death and disease. One of the reasons for this is that more importance is attached nowadays to the qualitative composition of the diet.

Another reason is that investigations have shown that qualitative malnutrition can occur in all classes of society. Yet another is that experiences from two world wars have attracted more attention to famines. In large areas of the globe — possibly in the majority — starvation or semi-starvation is something of a normal feature. Before the two world wars such situations had mainly arisen in the western hemisphere because of poor harvests. With better organization and transport facilities and an improvement in the standard of living it became possible to combat the results of poor harvests. The world wars once more gave rise to famine catastrophes and thereby constituted a series of terrible social experiments, showing the significance of this factor even today, affecting as it did entire nations even in the civilized areas of the western hemisphere.

Still another reason for the increasing interest in the influence of diet is the animal experiments that have been made. WARKANY and co-workers found that there was a higher incidence of malformations among the offspring of female animals when there were quantitative and qualitative deficiencies in the diet during pregnancy. Moreover, in their series the type of malformation appeared to vary according to the substance which was lacking. The factor that was finally considered to be responsible was a lack of riboflavin. It should, however, be borne in mind that the animals in their experiments were given such a markedly deficient diet that it was necessary to treat them with the utmost care if any offspring whatsoever were to be produced. This in no way detracts from the scientific value and interest of the experiments, but only raises doubts as to their applicability to conditions in man. A combination of a markedly deficient diet and extremely satisfactory care in other respects is scarcely conceivable in practice among human beings.

On the other hand, the objection that the results *per se* are inapplicable to man appears to be less justified. In principle this should be possible. There is, however, always the risk that hereditary traits may be present in a particular series. It is possible that their manifestation is facilitated by malnutrition. A more important objection is that some investigations have been

reported on human subjects in which the lack of riboflavin did not have the same effect as in WARKANY and co-workers' experiments on animals. One such study was made on Jewish subjects (BRAUN et al.), the riboflavin deficiency being estimated by its excretion in the urine. The subjects were divided into four different groups according to the riboflavin content. BRAUN et al. were unable to demonstrate any malformations in the offspring that could be attributed to a riboflavin deficiency in the mother's diet during pregnancy.

When considering the possible effect of nutritional deficiencies the following distinction must be made. Such a deficiency may be a general one, applying to all the components of the diet more or less impartially, or it may only apply to one particular component which there is reason to believe may be of importance for foetal development. Examples are proteins, certain vitamins and salts. Experiments on human subjects along the lines of those made on animals are obviously impossible. The main methods available are the following.

1. In cases of poor foetal development a retrospective analysis can be made of the mother's diet during pregnancy. An attempt can then be made to ascertain which dietary deficiencies are responsible. This method is always unreliable. It is greatly hampered by the source of error mentioned earlier, namely, that individuals living on a markedly deficient diet are usually subject to other unsatisfactory conditions such as cramped housing, financial difficulties and ignorance. Moreover, a control series must be always more or less arbitrarily selected.

2. A more satisfactory procedure from a scientific point of view is to reverse the procedure. One group is given supplementary food and the results are compared with those in a group of the same social standard but given no supplementary nourishment. The additions to the diet can be varied in different ways and the controls can be as adequate as the human organism permits.

3. Finally, a third way has been afforded by the chaotic conditions existing today, namely, the extensive malnutrition that has affected large sections of the human population as a

result of the world wars. As mentioned earlier, failure of the harvest has provided similar social experiments, although they have never been as thoroughly studied. The weakness of this kind of material is that it is too comprehensive. It is not possible to find groups of persons in the same social circumstances who are well-nourished for comparison with those who are under-nourished. The necessary control groups must be taken from periods before and after such occurrences.

Investigations have been made on many such series. The results must be considered contradictory to some extent. At times they are found to show a lack of agreement even in the same investigation, indicating that the material is unreliable.

In my opinion, one of the best studies of the effects of under-nourishment on a large group of the population is that published by SMITH, whose investigation covered a six-months hunger period caused by a transport strike in Rotterdam and the Hague from the autumn of 1944 to the spring of 1945. STUART and his collaborators have done excellent work on the effect of additions to the ordinary diet and BURKE's retrospective studies of the mother's diet during pregnancy are also of great value. In any investigation of this type it is, however, necessary to take into account dietary conditions before pregnancy and also at what stage of pregnancy the lack occurred and how long it lasted.

The results of all these investigations may be summed up as follows. Malnutrition during pregnancy can affect both the pregnancy and the development of the foetus. The most striking effect of general dietetic deficiencies is that the woman is very much less likely to conceive. In SMITH's series, the fertility fell to one-third of the earlier incidence and 50 per cent of the women suffered from amenorrhoea. This may possibly be regarded as nature's own form of protection against the additional load of pregnancy on an undernourished woman and even as a protection against the conception of a child whose prognosis would be poorer than if the mother were adequately fed. SMITH found that both menstruation and fertility rapidly returned to normal when the dietary deficiencies were remedied.

As regards the child, undernourishment of the mother ap-

pears to affect both the weight and the length at birth, the former appreciably and the latter to a less marked degree. It may be mentioned that similar observations have been made in experiments on sheep. It has not been possible to note any definite influence on the incidence of spontaneous abortions, but this aspect of the situation is always difficult to assess. On the other hand, the incidence of premature births was usually increased in those series in which the birth weight was affected. No definite increase has been shown either in the incidence of neonatal mortality or stillbirths but the results have varied in different investigations. No rise in the incidence of malformations has been clearly demonstrated but this would require an extremely large series since it is low in man even under extreme conditions and therefore difficult to estimate. Thus, no one has as yet proved a relationship between congenital malformations in the human foetus and nutritional deficiency in the mother.

Lactation is another factor which must be considered to have a great, although indirect, influence on infant mortality. Malnutrition does not as a rule lower the incidence of breast feeding. It may, however, affect the quantity of breast milk and cause the flow to cease earlier. This is a common observation even when the malnutrition is only of moderate degree.

It can be asserted that the results of investigations made indicate that nutritional deficiencies during pregnancy are a possible cause of a subnormal birth weight and a lower degree of development in the foetus. They do not, however, justify the conclusion that they inevitably lead to unsatisfactory results of pregnancy. Furthermore, we do not know how far a correct diet is necessary to ensure an uncomplicated pregnancy and a child that is healthy at birth. If a deficient diet has any effect on the incidence of congenital defects it is presumably of more importance immediately before pregnancy and during its initial stages rather than later. With regard to the development of the foetal skeleton, on the other hand, the conditions during the later part of pregnancy are of great importance. It is possible, also, that the haemoglobin content and the number of red blood corpuscles may be affected by the same factor, although the

results will not usually be evident until the second or third quarter of the first year of life.

The question of the effect of a lack of certain specific substances in the diet must be left open at present. There does, however, seem to be some direct relationship between the birth weight and a certain minimum content both of total proteins and of some amino acids in the mother's diet during pregnancy. Protein appears to be of particular importance for the metabolism of phosphorus and calcium. Qualitative nutritional deficiencies can also give rise to a pre-eclamptic condition in the mother and thus affect her offspring. The influence of a lack of riboflavin on the occurrence of foetal defects has already been mentioned. It must, however, be pointed out that nature has a wonderful capacity for protecting the "parasite" — *i.e.*, the foetus — to a great extent, even at the expense of the mother.

A question that is nowadays of some social significance is the effect of the mother's age and the parity on foetal development. Social developments have led to some alterations in these respects. Thus, in the more highly educated social groups the mother is often older at the birth of her first child than is the case with a woman of the working classes. In addition, the former more often has only one child. This is due to the fact that marriage takes place at a relatively later age in groups who continue their education longer. This may possibly be of some importance from a point of view of racial hygiene.

For the past 200 years the population statistics in Sweden have been satisfactory. In the present connexion, those for stillbirths are the easiest to register and are therefore most reliable. I have found, in a computation of the rate from this source, that it is lowest for the youngest mothers and then rises steadily with the age of the mother. Thus, the risk of a 30-year-old woman giving birth to a dead child is about twice that for a 20-year-old. Calculated on similar material, the rate of stillbirths for first parities has been found to be higher than for second and third parities, and is lowest in the case of the last-mentioned. Fourth parities again have a higher rate than first parities. It is true that stillbirth is conditioned partly by mechanical and other

factors during parturition. But, as pointed out earlier, it can be assumed that stillbirth can to some extent be regarded as an indication that other weaknesses, associated with the age of the mother and the birth parity, can also occur.

A mother's illness may be transmitted to her foetus. Foetal variola was described as long as 250 years ago. Similar observations have been made in the case of malaria, yellow fever and febris recurrens. During the 1918 influenza epidemic, it was found that 30—50 per cent of the women who contracted influenza during pregnancy had miscarriages, stillbirths or infants who died early.

Illnesses during pregnancy have also been considered to cause foetal malformations. Syphilis was long believed to have such an effect. This has been contested by later writers who have had more adequate control material. Congenital tuberculosis is so rare that it is scarcely possible to draw any definite conclusions. On the other hand, tuberculosis is not uncommon during pregnancy. A comparison between the incidence of malformations in the children of such mothers and in those of healthy mothers should be able to provide some information. The question must at present be left open. This is partly because no particular attention has been focused on it until lately and few thorough studies of the subject have been made.

A new, and to some extent surprising, finding has been made fairly recently. In 1942, GREGG reported that German measles in the mother may result in malformation of her foetus. This opens up wide possibilities as to the relationship between virus diseases in pregnancy and foetal malformations. It appears, however, that there is only a real risk when German measles develops during the first six to eight weeks after conception. Furthermore, the risk of a malformation of the foetus on these grounds — as in the case of other such illnesses during pregnancy — appears to be considerably less than was at first supposed. A report recently published on a large Swedish series (GRÖNVALL & SELANDER) supports this view, as do the latest publications in the U.S.A. Some earlier authors stated that there was a 100 per cent risk of malformation of the foetus if the mother con-

tracted German measles during the first two months of pregnancy and a 50 per cent risk if this occurred during the third month. In the Swedish series the incidence was found to be one in 26 mothers with German measles out of a total of 24 519 pregnant women with various virus diseases. It may therefore be questioned whether, in the earlier reports, the illness really was German measles. However this may be, many other environmental factors may have played a rôle. The malformations in question were microcephalus, cataract, congenital heart disease and deafness.

During the past few years it has also been suggested that toxoplasmosis may cause congenital anomalies.

It has long been known that irradiation of the foetus with x-rays or radium can give rise to various kinds of malformations including microcephalus. This has been confirmed by the sequelae of the atomic bomb. It is also an established fact that irradiation of the sexual glands can cause anomalies. These appear to be mainly in the form of skeletal deformities, such as cleft palate, talipes equinus, hypomandibulism and cranial defects. Here as well, the stage of pregnancy at which irradiation is given appears to be of prime importance. It should be borne in mind that even therapeutic doses of x-rays or radium appear to be sufficient to produce such injurious effects.

The influence of such factors as ectopic gestation, adhesions of the amnion, an abnormal position of the foetus, placenta praevia, or a displacement of the uterus has been discussed, but no conclusions have been reached. The results of various investigations are contradictory and the view has been expressed that the forementioned anomalies themselves are possibly hereditary.

The effect of drugs is a very controversial question. This is particularly evident on the basis of their use as abortifacients. The foetus can definitely be injured by certain drugs, but to a lesser extent than we should be inclined to assume.

The newly born infants of diabetic mothers are known to be more liable to an early death than those of healthy women, particularly during their first days of life. It was long believed that the pancreas of the foetus deputized for the insufficient insulin production of the mother, and that this excessive output continued

for some time after birth, resulting in death from hypoglycemia. Recently, however, this view has been disputed. It must therefore be considered that the reason for the poorer viability of such infants is not yet known.

Heart disease and debilitating diseases in the mother appear to be of importance if they have a serious effect on her general health.

Various forms of albuminuria in the mother are extremely potent sources of injury to her offspring. The albuminuria of pregnancy or childbirth does not only give rise to stillbirth. It can also result in premature birth or in general delicacy in a child born at full term, even if its birth weight is normal. Every experienced pediatrician knows that such children continue for an appreciable time to have less resistance than those of women who have not suffered from toxemia.

Infectious diseases other than those caused by viruses can also play a rôle in the aetiology of foetal anomalies.

Of the social factors, illegitimate birth is, as mentioned earlier, one of the most outstanding. It is a well-known fact that unmarried women run a greater risk of the pregnancy terminating in spontaneous abortion, premature birth or stillbirth. If their children are born alive they are more likely to die during the neonatal period or in infancy than children born in wedlock. In an investigation that I made on a series of Swedish women I found that the incidence of stillbirths was 50 per cent higher in the case of unmarried than of married women of the same age. Compared with the forementioned effect of the age factor, this implies that illegitimate birth increases the risk of stillbirth to the same extent as an increase of 10 years in the age of the mother. The contributory factors are numerous. One is the financial aspect. The incidence both of stillbirths and of mortality is much higher in children of the poor than of the well-to-do. In a Swedish series from Stockholm, EDIN found that the number of stillbirths was twice as high in the group of the lowest incomes as in the highest (see GYLLENSWÄRD). Financial insecurity is, however, certainly only one of many other important factors although it is the easiest to estimate. This is also reflected in the incidence of pre-

maturity. In the forementioned investigation I also found that premature births were relatively twice as common among mothers with average incomes as among the wealthy.

Nowadays an extremely important social factor is that pregnant women, as well as mothers with young babies, very often work outside the home. How far this factor contributes to foetal and infant mortality and infant diseases has not yet been fully elucidated. There are, however, many indications that it has a detrimental effect. One such indication is the fact that the incidence of prematurity appears to have increased during the past ten years, coinciding with an increase in the number of working mothers. Moreover, judging by available data, this incidence appears to be higher in the cities than in the rural districts.

A further question of interest, parallel to industrial work, is the importance of the "flight from the countryside" — the crowding in built-up areas. Our knowledge of these matters is as yet very incomplete.

Since prematurity is the cause of up to fifty per cent of deaths in infancy it is obviously of tremendous social importance. It is scarcely an exaggeration to state that, in countries with a low infant mortality rate, the prevention of prematurity is the most important task in an endeavour to bring about a still further decrease in the number of deaths in early infancy. The facts put forward in this paper show that the problem can be tackled successfully. Moreover, it is evident that external factors that can be combated by means of social measures play an important rôle — possibly the most important — in the causation of neonatal deaths and illness in the first year of life.

Summary

Whereas the rate of infant mortality has decreased significantly during the past years, the rate of neonatal mortality has remained approximately the same. This is particularly apparent in the statistics of those countries with low infant mortality rates. In Sweden, for example, the mortality rate for the first week of life may be as high as that for the remainder of the entire first year. It is the writer's opinion that it should be possible to prevent a considerable proportion of these neonatal deaths.

The rates of neonatal mortality and of stillbirths, the two being closely associated, are higher among the children of mothers in the lower social groups. This suggests that the social condition of the mother during pregnancy is important in the development of a viable foetus.

The incidence of prematurity also is higher in the lower social groups, the importance of this being apparent from the fact that up to 50 per cent of infant mortality may be attributed to prematurity.

The writer considers two of the most important tasks of those interested in child welfare today to be those of preventing stillbirths and of decreasing the incidence of prematurity, and he feels that both social and medical measures can be used to advantage in those tasks.

Considerable interest has recently been focused on the possible rôles in foetal malformation of certain factors present during pregnancy. Many factors, some positive and some negative, present during pregnancy and/or infancy and possibly causing death or illness during the first year of life, are discussed and illustrated.

C. GYLLENSWÄRD: *Le rôle d'une alimentation déficiente, de maladies et de mauvaises conditions sociales pendant la grossesse comme cause de la mortalité du nouveau-né et de la morbidité pendant la première année.*

Tandis que le taux de la mortalité infantile a baissé de façon significative au cours des années passées, le taux de la mortalité néonatale est resté approximativement le même. C'est particulièrement apparent dans les statistiques des pays où le taux de mortalité infantile est bas. En Suède, par exemple, le taux de mortalité pendant la première semaine de la vie est presque aussi haut que pendant la première année toute entière. L'opinion de l'auteur est qu'on pourrait prévenir une quantité considérable de ces morts néonatales.

Les taux de la mortalité néonatale et des morts-nés (les deux étant associés étroitement) sont plus élevés parmi les enfants de mères vivant dans les groupes sociaux les moins privilégiés. Ce qui suggère que la condition sociale de la mère pendant la grossesse est importante pour le développement d'un foetus viable.

La fréquence de la prématurité est également plus élevée dans les groupes sociaux les moins évolués: la gravité de ceci résulte apparemment du fait que presque la moitié de la mortalité infantile peut être attribuée à la prématurité.

L'auteur considère que 2 des plus importantes tâches de ceux qui aujourd'hui s'intéressent à la puériculture, sont de prévenir la naissance de morts-nés, et de diminuer la fréquence de prématurité. Il trouve

en outre que l'on peut adopter avec avantage des mesures à la fois sociales et médicales pour satisfaire ces deux préoccupations.

On a mis dernièrement au point avec un grand intérêt les rôles possibles dans les malformations foetales de certains facteurs intervenant durant la grossesse. Beaucoup de ces facteurs, les uns positifs, les autres négatifs, agissant pendant la grossesse ou l'enfance, et causant peut-être la mort ou la maladie pendant la première année de la vie, ont été discutés et illustrés.

C. GYLLENSWÄRD: *Einfluss von Mangelernährung, Krankheiten und schlechten sozialen Bedingungen während der Schwangerschaft als Ursache von Neugeborenensterblichkeit und Morbidität im ersten Lebensjahr.*

Während der Prozentsatz der Säuglingssterblichkeit in den vergangenen Jahren merklich abgenommen hat, ist die prozentuale Mortalität Neugeborener annähernd dieselbe geblieben. Dies geht besonders deutlich aus den Statistiken von Ländern mit geringer Säuglingssterblichkeit hervor. In Schweden zum Beispiel dürfte der Sterblichkeitsprozentsatz für die erste Lebenswoche ebenso hoch sein wie für den Rest des ganzen ersten Jahres. Nach Ansicht des Verfassers müsste es möglich sein, einen beträchtlichen Teil dieser Todesfälle Neugeborener zu verhindern.

Der Prozentsatz der Sterblichkeit Neugeborener und der von Totgeburten, welche sich eng aneinander anschliessen, sind höher unter den Kindern von Müttern in den unteren sozialen Schichten. Dies lässt vermuten, dass die sozialen Verhältnisse der Mutter während der Schwangerschaft von Bedeutung für die Entwicklung eines lebensfähigen Fetus sind.

Auch die Frequenz von Prämatunität ist in den unteren sozialen Schichten höher. Die Wichtigkeit dieses Umstandes geht aus der Tatsache hervor, dass bis zu 50 Prozent von Säuglingssterblichkeit Prämatunität zugeschrieben werden können.

Nach Ansicht des Verfassers sind heute zwei der wichtigsten Aufgaben für alle, die an der Kinderfürsorge interessiert sind, die Verhütung von Totgeburten und die Verminderung der Frequenz von Frühreife; er ist überzeugt, dass sowohl soziale als medizinische Massnahmen erfolgreich in den Dienst dieser Aufgaben gestellt werden können.

Grosses Interesse hat man neuerdings der Frage gewidmet, welche Rolle gewisse während der Schwangerschaft vorhandene Faktoren möglicherweise für fetale Missbildungen spielen können. Viele Faktoren, sowohl positive als negative, welche während der Schwangerschaft und

(oder) des Säuglingsalters vorliegen und möglicherweise Tod oder Krankheit im ersten Lebensjahr verursachen können, werden besprochen und beleuchtet.

C. GYLLENSWÄRD: *Papel desempeñado por una nutrición defectuosa, enfermedades o malas condiciones sociales durante el embarazo como causas de mortalidad neonatal o de enfermedad durante el primer año de la vida.*

A pesar de que la cifra de mortalidad infantil ha decrecido de un modo significativo durante los últimos años, la proporción de mortalidad neonatal ha permanecido aproximadamente la misma; este hecho es particularmente evidente en las estadísticas de los países con cifras bajas de mortalidad infantil. En Suecia por ejemplo la cifra de mortalidad durante la primera semana de la vida puede ser tan elevada como la correspondiente al resto del primer año, en opinión del autor sería posible prevenir en considerable proporción esta mortalidad neonatal.

Las cifras de mortalidad neonatal y de nacidos muertos ambas íntimamente asociadas son mayores entre los niños de madres pertenecientes a grupos sociales pobres; ello sugiere que las condiciones sociales de la madre durante el embarazo son importantes para el desarrollo de un feto viable.

La frecuencia de la prematuridad es también más elevada en los grupos sociales bajos, la importancia de ello se desprende del hecho que hasta un 50 % de la mortalidad infantil puede ser atribuida a la prematuridad.

El autor considera que dos de las más importantes tareas de cuantos están interesados hoy día en la salud de la infancia son, la prevención de nacidos muertos y la disminución de frecuencia de la prematuridad y preconiza que medidas tanto sociales como médicas deben ser usadas ampliamente en estas tareas. Recientemente ha despertado considerable interés la posibilidad de que ciertos factores presentes durante el embarazo puedan desempeñar un papel en la aparición de malformaciones fetales. Se discute y se aportan gráficas sobre algunos factores ya positivos o negativos presentes durante el embarazo y/o durante la infancia y posibles causantes de muerte o enfermedad durante el primer año de la vida.

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Epidemic Infantile Diarrhea and Vomiting

A Clinical-bacteriological Study with Special Reference to Bact. Coli Neapolitanum (B. C. N.), the Spreading of the Disease as an Air-borne Infection and to its Treatment with Aureomycin

by

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Introduction

Epidemic infantile diarrhea and vomiting has been arousing the interest of pediatricians and bacteriologists for a long time. Many attempts have been made to isolate a specific agent. In America, several investigators hold that they have found a virus (2, 7, 26, 28, 29), and among the more recent investigations those of LIGHT and HODES (28, 29) have brought out features of particular interest. These authors succeeded in transferring the infective agent to young calves, which began to have diarrhea with mucus and blood present in the stools after an incubation time of two to four days. Further, neutralizing antibodies against the infective agent were demonstrated in four of the affected children.

The majority of workers, however, consider that a micro-organism is the infecting agent, and *Staph. aureus* has been attributed a significant rôle in several epidemics (4, 8, 9, 10, 12, 15, 27, 34, 37). *B. coli* (1, 11, 13, 31, 35). *Ps. pyocyanea* (14) and *enterococci* (17, 39) have also been examined as possible agents.

During the past few years particular interest has been attached to a *Bacterium coli* strain, *Bact. coli neapolitanum* (abbreviated to B. C. N. in this paper).¹

This type of strain was mentioned first in connection with infantile dyspepsia by British authors (5, 6, 18, 19, 32, 36), and subsequently in American, Dutch (3), Danish (22) and Swedish reports (16, 30). In particular, the strain has been demonstrated frequently in connection with epidemics that have broken out in institutions, such as children's hospitals and day nurseries. The clinical picture in these outbreaks has been remarkably similar — viz., pronounced loss of weight, anorexia, toxaemia, diarrhea and vomiting, severe dehydration and a tendency to relapse. Mortality has often been high. As regards the treatment, streptomycin has been tried out by HOLZEL, MARTYN and APTER (20), but no specific therapeutic effect was achieved. ROGERS, KOEGLER and GERRARD (33) report encouraging results with chloramphenicol.

The present paper describes a series of 62 cases of epidemic infantile gastro-enteritis treated at the Sachs' Hospital for Children during the autumn of 1949 and the winter and spring months of 1950. Two outbreaks occurred in the Hospital during the autumn of 1949. Aureomycin treatment was tried, with encouraging results, and the experience gained with this antibiotic will be described. An investigation into the significance of air-borne and dust infections in hospitals has been in progress for several years at the Sachs' Hospital for Children. As epidemic infantile dyspepsia often occurs as a hospital epidemic the possibility that it may have been the result of an air-borne infection will also be examined in this paper.

Methods

Bacteriological methods. For the examination of bacteria from the respiratory tract samples were taken both from the throat and from the mucous membrane of the nose. Swabs of the usual type were used. In transport, the swabs were enclosed in inclined agar tubes, to protect them

¹ Strains of this type have been described under various names, such as *Bact. coli* D 433, *Bact. coli* α type, *Bact. coli* B.G.T., and *Bact. coli* Bray. KAUFFMANN (21) classified the strain as O 110 B 4 in Kauffmann-Vahlne's coli antigen list (21, 38).

from drying up. The feces samples were taken with testing material of the usual type, in tubes, with an aluminium spoon. Rectal swabs were not used. In the examination of the air, sedimentation plates were placed at the same height as the beds and exposed for a period of twelve to twenty-four hours. Milk, thermometers and rubber teats were examined by making smear cultures and also, after cultivation, in an enriched medium for twenty-four hours.

Agar plates, containing 10 per cent horse-blood, were used as the basic culture medium for all the bacteriological work, and Conradi-Drigalski's "blue agar plates" as the selective medium for the isolation of coliform bacteria. An important point to observe is that the layer of culture medium in the sedimentation plate should be thick and slightly damper than usual. Ordinary broth, with 0.1 per cent of glucose, was used for enrichment.

Serological methods. The serological examinations were carried out in accordance with the technique elaborated by KAUFFMANN, KNIPSCHILD and VAHLNE (21, 23, 38). According to these authors, the following antigen components are distinguishable in coliform bacteria. The O antigen is the somatic or cell body antigen; the K antigen, the capsular antigen; the H antigen, the flagellate or ciliary antigen. The B. C. N. strain that has been described in connection with epidemic gastro-enteritis is usually non-motile but has the capsular antigen. In the present investigation, the O and K antigen components were diagnosed first. Sera were produced from a test strain which was kindly placed at our disposal by Dr. Joan Taylor, England. The preliminary diagnosis was made by agglutinating colonies that looked suspicious in concentrated K sera on a slide. The bacterial colonies in question did not have a sufficiently characteristic appearance to enable them to be distinguished from other types of coliform bacteria when the plate was being examined. It was therefore necessary to examine several colonies from each culture serologically; at least 5—10 colonies were tested as a rule, usually from the so-called blue agar plate. In particularly suspicious cases, 5—10 colonies from the blood agar plate were also tested. The typical K agglutination, which takes place within a few seconds, is readily observable. Colonies that agglutinated on a slide were grown in pure culture in broth containing 0.1 per cent of glucose for twenty-four hours at 37° C. The "antigen" obtained in this way was heat-killed for 1 hour at 100° C, after which tube agglutination against O serum was carried out in accordance with the usual serological methods. The condition set for accepting the diagnosis was that both O and K antigen components must be demonstrable in the suspected strains. The B. C. N. strains that were isolated were re-examined for the flagellate antigen component by passage in semi-solid agar in U-tubes. In the case of motile strains, the H antigen was typed on the basis of the 22 H types mentioned in KAUFFMANN-VAHLNE'S list (38) and the 8 H types that have been iso-

lated from calves by WRAMBY (40). Finally, all the B. C. N. strains were examined biochemically with the aid of the so-called Imvic test (indol, methylred, Voges-Proskauer, citrate), and they were also studied from the aspect of their power to produce H_2S and to liquefy gelatin.

The Scope of the Tests

In the infants with diarrhea and vomiting, samples were taken at the onset of the illness and subsequently at least three times a week. At least two to three samples were taken in all cases, and even if the first sample gave a negative result this was not considered sufficient to justify a negative etiological diagnosis. In most of the children given aureomycin, samples were taken daily. From the control series, samples were taken on admission and then twice a week. All members of the staff working in the wards were kept under constant observation. This applied to physicians, nurses, assistants, probationers and wet-nurses. Samples were taken when they began their service in the wards and thereafter once a week. Some of the staff only served for a short time at the Hospital, and from these, only one or two samples were obtained.

The Hospital Buildings

In the beginning, the investigation was conducted in the older building attached to the Sachs' Hospital for Children. The plan of the wards in this building has already been described in an earlier publication (25). With a view to preventing air-borne nosocomial infections the wards were planned on the open-box system. In practice, this system furnished extremely limited possibilities for the isolation of highly infectious patients. Since November 1949, newly-built wards have been in use at the Hospital, and the investigation was continued in this new isolation department during the winter and spring of 1950. This department provides excellent opportunities for effective isolation, and this has been of considerable significance in the prevention of nosocomial infections. A plan of the department is shown in fig. 1.

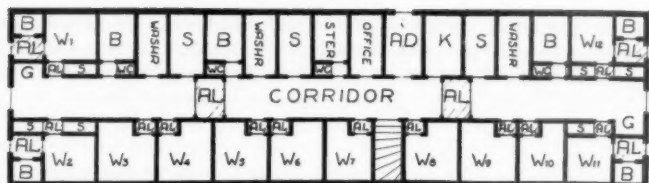


Fig. 1. The isolation department at the Sachs' Hospital for Children.

W 1—W 12 = Ward units
 A. L. = Air lock
 B = Bath
 S = Store
 G = Gowns

Ster. = Sterilizing room
 K = Kitchen
 Office = Registration office
 A. D. = Admission of patients

The wards and utility rooms are grouped along both sides of a central corridor which extends the full length of the department. The department is divided into three parts with the help of so-called air locks and the wards can only be entered through an air lock. At both ends of the building there are complete isolation rooms with baths, and so on. Entrance to these is also possible from outside the hospital building, and thus children with highly infectious diseases do not need to pass through the wards in order to reach these rooms. The wards accommodate one to two children. To provide for ventilation, each ward has a separate air-conditioning system. The air is changed approximately eight times an hour. The daily routine in the wards has followed the pattern described in connection with earlier investigations. Facilities for washing and disinfection of the hands are available in the wards themselves and also in the air locks separating the different wards and in those serving as entrance to the isolation rooms.

Material

Clinical group. The clinical material is composed of 62 children with epidemic gastro-enteritis who were treated at the Hospital and in whom B. C. N. bacteria were demonstrated. Of these, 41 cases originated from two outbreaks in the old building during the period July—November, 1949. The first took place during July—September, and B. C. N. bacteria were demonstrated in 20 children altogether, which was responsible for 21 cases, took place in October—November. No fresh outbreaks occurred since the new wards have been opened, and during the six months that the investigation was in progress in the new isolation department, only two

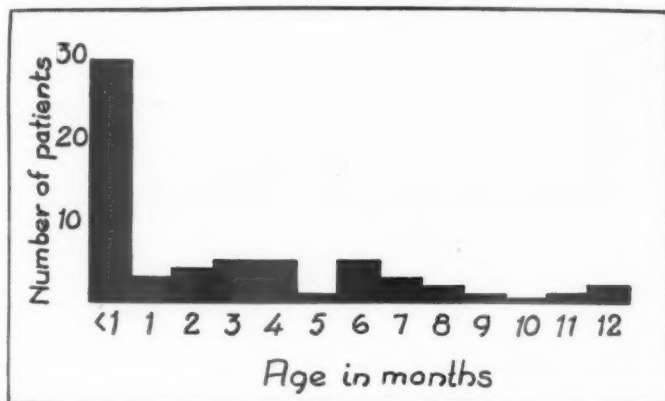


Fig. 2. Age distribution in the clinical group.

nosocomial cases of gastro-enteritis due to B. C. N. occurred. Of the remaining 19 cases, which had not occurred in the Hospital, 12 had been referred after falling ill at a day nursery and 2 from a home for post-natal care. Four had been infected at a maternity hospital and one while under treatment at an orthopedic clinic. As regards the age distribution, which is shown in fig. 2, all children except one were less than one year old. The exception was a child aged one year and two months. He had contracted the disease in hospital. A feature of particular interest was that of the 28 infants that were younger than one month, 12 were in Hospital because of prematurity.

The control group. This group consisted of children who were treated in Hospital for other reasons during the time the investigation was in progress and who did not develop diarrhea or vomiting. There were 346 children in this group. The age distribution in the control group is shown in fig. 3, and it will be seen that the majority of the children were infants or children up to the age of 3 years; there were also a few children aged 6—7 years.

Staff. A total of 151 members of the staff were examined. B. C. N. was isolated in the feces in only one probationer and in

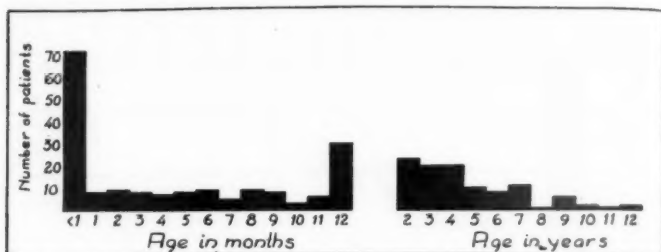


Fig. 3. Age distribution in the control group.

one physician. On only one occasion was *B. C. N.* found in the respiratory tract — in a nurse. The probationer in whose feces the bacteria were demonstrated had mild gastro-enteritis when the investigation was carried out.

Clinical Manifestations

The clinical features were in the main the same as those described by Anglo-Saxon authors in connection with similar epidemics. We shall therefore confine ourselves here to making a short survey of the chief symptoms. As a rule, the incubation time is difficult to state exactly, but an approximate time was established for 32 children. In no case was it longer than 20 days, and it was never less than 3 days. In general, it varied between 8 and 12 days. The dominating clinical sign at the onset of the disease was diarrhea of varying degrees of severity, usually accompanied by vomiting. A moderate degree of fever, varying between 38° and 39° C was a common occurrence while high fever of over 40° C was uncommon. In the severe cases the stools were watery and projectile, and in some instances the attacks of diarrhea were as many as 30–40 a day. The stools in many cases had a characteristic seminal smell. Considerable loss of fluid occurred in connection with the frequent attacks of diarrhea; in the severe cases this was between 500 and 1 000 grams and threatened the life of the patients. The general condition of these patients became serious. They went into a state resembling shock, with an ashen skin and pronounced signs of de-

hydration. As has already been noted (fig. 2), many young infants contracted the disease. Thus, as may be seen from table 1, the weight of the children was, not infrequently, already low at the onset of the disease.

Table 1.

Weight at onset in 58 children in the clinical group.

Weight in grams	No. of children
1 000—1 500	4
1 500—2 000	4
2 000—2 500	4
2 500—3 000	7
3 000—4 000	7
4 000—5 000	4
> 5 000	25
Total	58

A not inconsiderable number of children weighed less than 2 000 grams at the onset, and in some cases the weight was even below 1 500 grams. As found in epidemics reported by other authors, the severest dyspepsia occurred in newborns, the very young infants and the prematures. It is interesting to note that the very young infants and prematures had been receiving breast milk as their basic food before they contracted the disease. In the whole material, two-thirds of the cases could be said to be severe or moderately severe and one-third mild. A number of deaths occurred during the first epidemic, before aureomycin treatment was instituted. After the inception of aureomycin therapy as a routine measure there were no deaths. In order to illustrate the clinical picture in more detail accounts of two typical cases are given here.

538/49. A newborn girl was admitted because of prematurity; weight at birth, 1 550 g. Nothing of note occurred during the first week in Hospital. In the 11th day after admission there was slight diarrhea, with a failure to gain weight. Penicillin and "elkosin" therapy was started and aminosol glucose and Darrow's solution given subcutaneously. During the subsequent days there was a temporary improvement with a gain in weight. On the 23rd day there was a sudden exacerbation with increasing

diarrhea. Streptomycin therapy was started and fluids given intravenously. The condition nevertheless continued to deteriorate; the diarrhea became watery and extremely severe, and death ensued on the 40th day. Pure cultures of *B. C. N.* were found in the stools seven days before death. Necropsy revealed no pathological condition in the intestines, but there was bilateral bronchopneumonia and bilateral purulent mastoiditis; clinically, the infant died from an acute intestinal infection.

577/49. A newborn boy was also admitted because of prematurity; weight at birth 2 370 g. Initially there was nothing of note but on the seventh day in Hospital frequent stools with loss of weight developed. Sulphonamide was given by mouth, penicillin intravenously, plentiful fluids (Darrow's solution and aminosol glucose) subcutaneously, and breast milk, arobon, and glucose solution by mouth. There was no improvement; on the contrary a marked exacerbation occurred on the 13th day after admission, with pronounced symptoms of shock, bad colour, depression of the fontanelle, appreciable loss of weight, and 10 to 13 watery, violent, and mucous stools a day with frequent vomiting. He was put in an oxygen tent, streptomycin being administered by mouth and serum intratibially. During the following week his general condition varied, but there was no marked improvement. The administration of sulphonamide and antibiotics was therefore stopped. *B. C. N.* was found in the stools on the 17th day of illness and in the nose and stools on the 28th day. An intravenous cannula had been inserted earlier (on the 20th day of illness), and during the next six days he was mainly nourished in this way. There was then a rapid progress with a considerable gain in weight and an improvement in the stools. The improvement continued and the patient was discharged from Hospital with a weight of 2 560 g.

Treatment

During the first few days of illness all infants with gastro-enteritis received plentiful supply of fluid (plasma, aminosol glucose, Darrow's solution), administered either subcutaneously or intravenously, as well as Arobon solution or carrot soup by mouth. The basic diet was breast milk. Penicillin and sulphonamide compounds were tried but they had no noticeable effect on the dyspepsia. As ROGERS, KOEGLER and GERRARD have also pointed out, gastro-enteritis developed in several cases during the course of the penicillin and sulpha treatment. Streptomycin was also tried in 17 cases but it had no specific therapeutic effect. In this respect, our results tally with those reported by HOLZEL, MARTYN and APTER, and by ROGERS, KOEGLER and GERRARD.

Treatment with Aureomycin

The administration of aureomycin was started as a tentative measure in October 1949, and preliminary reports on the results obtained in these first cases has already been published (30). It was demonstrated that the B. C. N. strains were sensitive to this antibiotic. Resistance tests were made in thioglycollate broth and the recordings were read after 8—10 hours' incubation at 37° C. A total of 254 strains have been tested up to the time of writing. The resistance varied inappreciably, and lay between 0.08 and 0.32 $\mu\text{g/ml}$; with a few strains it was up to 0.64 $\mu\text{g/ml}$. No increased resistance was noted in the course of treatment. Aureomycin was given by mouth six times a day, in doses calculated on the basis of 70 mg per kg of body weight a day. In the beginning, in the old hospital building where the risk of reinfection was considerable, the treatment was continued until the patient was discharged from the Hospital and the final result was checked up in the out-patient department. A number of healthy infants in the wards, especially prematures, were given prophylactic treatment at that time. Later on, when the facilities for isolation were better, the treatment time was gradually decreased and trials were even made with as short a treatment time as two days. From the standpoint of carriers, this latter time proved to be too short, and we are now treating our patients, even the mild cases, over a period of at least five days.

The clinical improvement noted in connection with the treatment was in many cases striking. Even in severe cases, a rapid improvement occurred during the first few days, and after 4—5 days' treatment the clinical signs and symptoms of the disease had almost entirely disappeared in many instances. A total of 32 children in the clinical group have been treated up to the present, and during this time there have been no deaths. Only in a few (isolated) cases it was necessary to have recourse to intravenous administration of fluid in order to reinstate the fluid balance in the severe cases. In addition to the children with gastro-enteritis eight healthy carriers as well as the physician and probationer who became carriers while working in the wards, received treatment. None of the

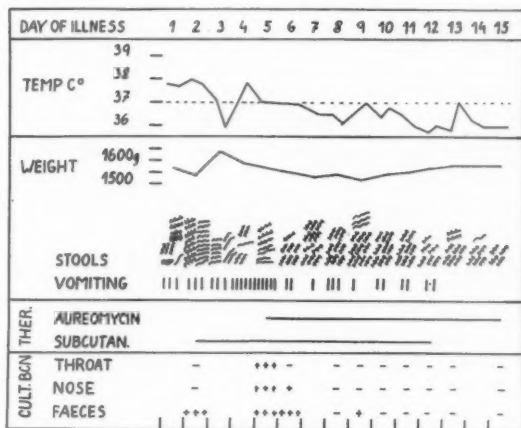
children who were treated prophylactically contracted the disease. In order to illustrate the results of the treatment a short description of a few typical cases is given.

Case Reports

Case 1. Record no. 647/49. A male infant, born Sept. 30th, 1949, was admitted because of debility shortly after birth. Weight at birth 1 480 g. On admission he was found to be a fine premature boy presenting nothing of particular interest. He was put on breast milk and also received, in addition, aminosol glucose. Penicillin was administered by mouth as a prophylactic.

During the first two weeks he developed normally. Seventeen days later he suddenly began to suffer from diarrhea with vomiting and frequent watery stools (10—18 a day) yellow in colour and with a stale smell. The general condition steadily deteriorated; the abdomen was moderately distended and the colour ashen-grey. Streptomycin treatment by mouth was begun and some of the breast milk was replaced by arobon. Additional fluid (aminosol glucose, Darrow's solution) was given subcutaneously three times a day. As no improvement had occurred at the end of three days and B. C. N. was demonstrated in the stools after cultivation, aureomycin therapy was instituted (on the 21st day), in doses of 25 mg 6 times a day. At the same time, the penicillin and streptomycin treatment was discontinued. Twenty-four hours later the stools were semi-solid, but were still frequent (7—11 a day). Only one subcutaneous infusion a day was necessary. From the 25th day on when the weight was 1 520 g, the infant began to show fairly good weight increases. By Nov. 2 the general condition was thoroughly satisfactory. The only abnormal feature was that the skin all over the body was rather dry, and on the back and around the anus was inflamed and papuliferous. The infant continued to develop normally.

Case 2. Record no. 686/49. A girl, born Oct. 6th, 1949, was admitted direct from the maternity hospital because of debility. Weight at birth 2 090 g. She was a twin. On admission she was found to be a fine premature baby presenting no features of particular interest. She was put on breast milk and aminosol glucose, and developed normally during the first two weeks. She then began to have fairly frequent stools, which became watery on Oct. 24. She had vomiting attacks and lost weight, looked pale and drawn, but was nevertheless fairly lively. Cultures from the faeces revealed that B. C. N. was present, and aureomycin treatment was begun on Oct. 25 (fluid was administered subcutaneously and carrot soup also given). Twenty-four hours later the stools were semi-solid. The infant ceased to lose weight, and after Oct. 29 a satisfactory increase in weight was noted.



Case 1.

Explanation of the signs

Stools

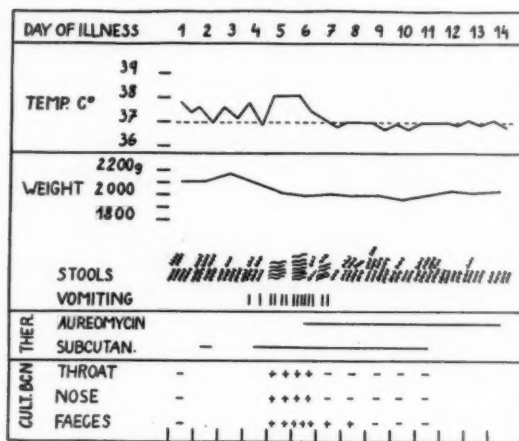
- ≡ indicate watery projectile diarrhea, the number of lines denoting the frequency.
- ||| indicate mucous stools.
- |||| indicate porridgy stools of normal appearance.
- |||| indicate stools of normal firm consistency.

Vomiting

- |||| denotes vomiting attacks, the number of lines indicating the frequency.

Cult. B. C. N.

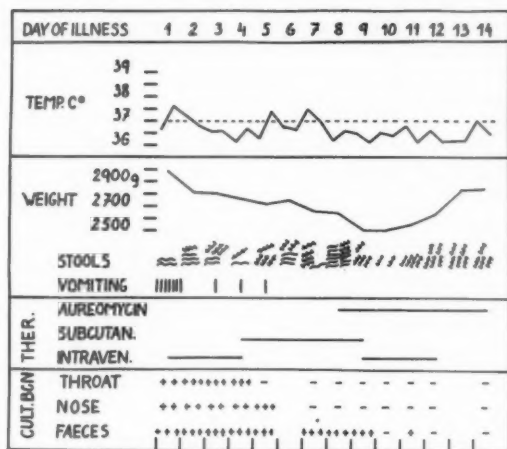
- +++ denotes that B. C. N. was present in plentiful numbers.
- ++ indicates that B. C. N. was present in moderate numbers.
- + indicates that B. C. N. was sparsely represented (after cultivation in an enriched medium).
- indicates that B. C. N. was not found (after cultivation in an enriched medium).



Case 2.

A little later on, the skin around the anus became dry and slightly infiltrated. Improvement continued, and the general state of health was soon excellent. The infant gained steadily in weight and was sent home in a satisfactory condition.

Case 3. Record no. 744/49. A boy, born Oct. 2, 1949, was admitted on Oct. 24 because of gastro-enteritis. He was found on admission to be an infant of three weeks who had shown a tendency to vomit since he was born. During the week before he was admitted the vomiting attacks had increased and the stools contained mucus. His weight at birth had been 3 430 g. but when admitted he was only 2 790 g. Examination in the Hospital revealed that he was dehydrated and pale, with slight peripheral cyanosis. The turgor was poor. Thrush was present in the oral cavity. The abdomen was distended and blood oozed from the umbilicus. There was violent watery diarrhea and frequent vomiting. He was given a small amount of carrot soup by mouth but for the rest, nourishment was administered intravenously. A couple of days later the abdomen was less distended and the vomiting attacks had decreased, but despite a plentiful supply of fluids he got worse and steadily lost weight, the lowest weight recorded being 2 510 g on Nov. 2. Aureomycin therapy was begun on Nov. 1, after B. C. N. were isolated from the stools. (These had also been present on the day of admission.) By Nov. 3 the stools had become normal and the general condition was satisfactory. In the course of the aureomycin



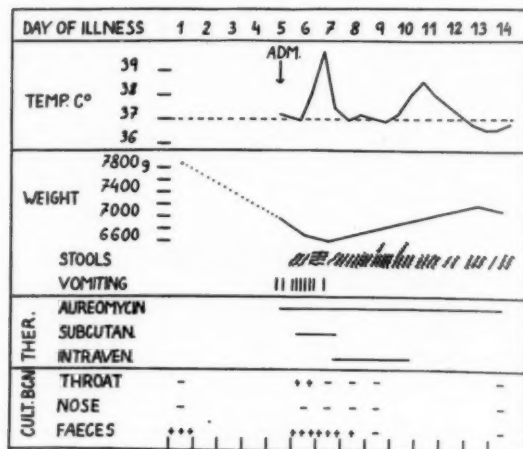
Case 3.

treatment the skin on the face became dry and tended to peel, and in the region of the buttocks there were signs of infiltration. The infant was discharged in good condition on Nov. 27, weighing 3 100 g.

Case 4. Record no. 912/49. A boy, born May 12, 1949; weight at birth 3 160 g. Admitted on Dec. 19, 1949. Weighing 6 920 g.

This infant, aged 7 months, had previously been treated in the Hospital for otitis and eczema. Some of the infants in the wards had been found to be harboring B. C. N. and samples for culturing were therefore also taken from this patient. B. C. N. was found in a feces sample on the day of his discharge. While in Hospital, the patient's stools had been normal, but about a day after he left he began to have diarrhea and vomiting and was therefore re-admitted.

On admission he was found to be highly dehydrated and in a severe state of intoxication. A recurrence of the otitis also seemed imminent. He was passing loose stools with the typical seminal smell, and had frequent vomiting attacks. In addition to a blood transfusion and the subcutaneous administration of fluids, aureomycin treatment was also begun in view of the bacteria found in the feces. 25 mg was given by mouth 6 times a day. As the vomiting interfered with the administration of aureomycin, most of the nourishment that was being given by mouth was stopped and an intravenous transfusion set up. The infant gradually began to



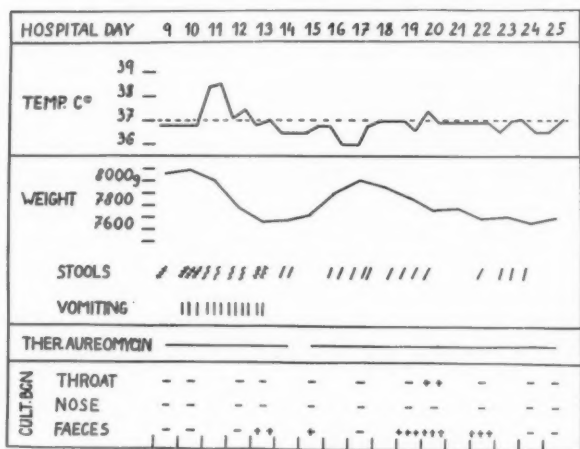
Case 4. ADM = Admission to the hospital.

improve, and three days after admission his condition was satisfactory. Within 4 days the stools were firmer and after another 2 days they were normal. In the course of the aureomycin treatment mild eczema broke out again, and the skin around the anus looked dry and rough. The aureomycin was withdrawn two weeks after admission, and the infant was sent home one week later, improving steadily. The B. C. N. cultures were positive during the first three days of treatment but thereafter were consistently negative.

Case 5. Record no. 23/50. A 1-year-old girl, born Dec. 8, 1948; weight at birth 3 270 g. Admitted Jan. 5, 1950; weight on admission 8 106 g.

This child was sent to the Hospital from a home for infants where the presence of B. C. N. had been established among both children and staff at the time when our patient fell ill. Seven weeks before being admitted the patient had had diarrhea with vomiting and frequent mucous stools over a period of a few days. About 3 weeks before being admitted to the Sachs' Hospital for Children she again had loose mucous stools. On this last occasion she received aureomycin in conjunction with the staff and other children at the infants' home for one week. As B. C. N. was found in the cultures 4 days after the therapy was terminated the child was admitted for further treatment with aureomycin.

On admission the child presented no unusual features and this continued for the first 10 days. Aureomycin, in doses of 10 mg, was given 6

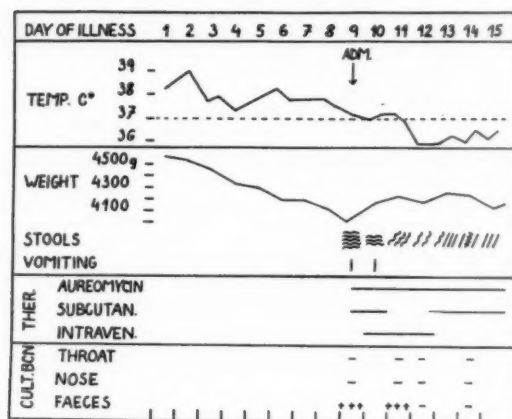


Case 5.

times a day by mouth (later, also Becozym), and the child received the usual infants' diet. At the end of 10 days the temperature rose to 38.5° C, vomiting attacks occurred and there was a loss in weight amounting, during the three days the exacerbation lasted, to 400 g. The stools were normal, however. Three days later, the symptoms had abated but the cultures, which, during the first 10 days, had failed to reveal the presence of B. C. N., now became positive again. At this time the cultures from all the other patients in the ward were negative. In an adjoining room, however, one of the patients (59/50) had a positive B. C. N. culture. The child's cultures alternated between positive and negative several times during the next two weeks and then became consistently negative. Apart from the exacerbation lasting three days the child had no symptoms while in hospital. While on aureomycin therapy her skin became rather dry and irritated, especially around the anus, but this disappeared after she started taking Becozym. She was sent back to the infants' home six weeks after admission. Because of the risk of reinfection the aureomycin was continued for a time.

Case 6. Record no. 59/50. A 4-month-old girl, born Sept. 15, 1949; weight at birth 2 415 g. Admitted Jan. 14, 1950; weight 4 080 g.

This child had been at a home for infants where cases of gastro-enteritis associated with B. C. N. had occurred in the months immediately preceding the time when the patient fell ill.



Case 6. ADM = Admission to the hospital.

The infant had begun to have attacks of vomiting and diarrhea, with a temperature of up to 39° C, 8 days before admission to the Sachs' Hospital. She was put on the treatment usually given for gastro-enteritis and improved during the first 7 days. On the 8th day of illness there was a marked exacerbation and after repeated vomiting attacks a state of severe dehydration developed. The weight lost was 550 g, calculated from the first day of illness.

She was admitted on the 9th day of her illness, and was found to have markedly lowered turgor, with depressed fontanelle and signs of mild intoxication. She was passing loose, foul smelling, mucous stools of a yellowish-green colour. She was given penicillin, fluids subcutaneously and intravenously, and carrot soup by mouth, and in addition, aureomycin therapy, 75 mg 6 times a day by mouth, was instituted after feces samples had been taken for cultures. Two days after admission a considerable improvement was noted, and after a further 3 days the general condition was satisfactory in spite of slightly lowered turgor and stools containing a little mucus.

The child's skin became rather dry and infiltrated, especially on the buttocks, during the aureomycin therapy, but this trouble disappeared after the administration of Becozym, although the dose of aureomycin was still the same. As the child was to be sent back to an infants' home she was kept on aureomycin (in conjunction with Becozym) till she was discharged, with a view to decreasing the risk of reinfection. The infant had B. C. N. in her stools for the first two days in hospital, but all subsequent samples were negative.

Side-Effects Connected with Aureomycin Treatment

When aureomycin was administered, in the doses indicated above, to healthy infants as a prophylactic measure, sluggishness and tendency to vomit were noted in nearly every case. The stools not infrequently changed their character and became slightly loose. After about ten days' treatment without the simultaneous administration of extra vitamin B there were pronounced skin manifestations. The skin became dry and infiltrated, there was intense redness and a tendency to peel. These features were also noted in the sick children. The skin manifestations were generalized in a few cases but in most of the infants they were localized in the genital and anal regions, the buttocks and the face. These symptoms disappeared entirely when the B complex was administered, even though the doses of aureomycin remained unchanged over a long period. The symptoms failed to appear if extra vitamin B was supplied in good time in association with the start of the aureomycin treatment.

Results of the Bacteriological Examinations

Feces. Clinical group. B. C. N. was found in all the sick children in the clinical group. 915 specimens were examined. The bacteria were often present in pure cultures during the acute stage of the disease, and subsequently gradually decreased in numbers and then disappeared entirely. Among those children who were not treated with aureomycin the presence of B. C. N. was demonstrated long after the symptoms had completely disappeared, and in some cases it was still found 3—4 months after treatment in Hospital. Another micro-organism found was *Staph. aureus*, which was demonstrated in roughly one-half of the infants. As a rule, colonies were few; only in a few infants was it present in any numbers. There was no connection between its occurrence in the intestinal flora and the clinical symptoms. Enterococci were a common finding, being isolated from a little over one-half of the children. *B. proteus* was found in four infants, and in three, *Ps. pyocyanea* was present.

Feces. Control group. In the control group, comprising 346 children, 905 specimens were examined. In addition to coliform organisms, which were demonstrated in all instances, *Staph. aureus* and enterococci were found to the same extent as in the clinical group. *B. proteus* was isolated from 7 children and *Ps. pyocyanea* from 14. The presence of B. C. N. was established in 12 children. Of these, only 3 had become infected while in Hospital, all of them in connection with the second outbreak. The frequency of carriers that arose in a Hospital environment infected with B. N. C. was therefore 0.9 per cent. The remaining healthy carriers were encountered in connection with investigations into environmental conditions conducted at one of the infants' homes and at the maternity hospital from which clinically ill children had been sent in. They were admitted to hospital before treatment with aureomycin had been started.

Feces. Staff. From the hospital staff 334 samples were examined. The bacterial flora showed no divergence from the normal picture, and the examinations served mainly as a check-up on the presence of B. C. N. The micro-organism in question was found on two different occasions in the probationer who became ill, while the physician, who was quite well, was only a carrier on one occasion.

Respiratory tract. One of the most interesting problems that arises in connection with the study of epidemics and infections in hospitals is to find out which persons spread the infective agent to their surroundings. We have at this Hospital confirmed Hamburger's investigations, which showed that persons harboring the infective agent in the nose are especially liable to spread the infection and thus must be regarded as dangerous carriers. In the present investigation, it was found that coliform bacteria were a common occurrence in the respiratory passages. In the clinical group, among 2 010 cultures, coliform bacteria were found in the throat 402 times and in the nose and throat 220 times. Among the 2 140 cultures from the control series; coliforms were demonstrated in the throat 447 times and in the throat and nose 341 times. Finally, in the

1 446 cultures from the staff, coliforms were isolated from the throat 92 times and from the throat and nose 141 times. In view of these results, especially the fact that coliform bacteria were isolated so often from the nose, it seemed of interest to investigate whether any of the coliform bacteria were identical with B. C. N. The results of the serological typing with B. C. N. are shown in table 2.

Table 2.

Results of typing with B.C.N. in those cases where coliform bacteria were demonstrated in the respiratory tract.

	Total	B.C.N. in the throat only	Other coliforms in the throat only	B.C.N. in the throat and nose	Other coliforms in the throat and nose
Clinical group	51	5	12	20	14
Control group	144	0	92	1	51
Ward staff	63	0	9	1	53

As may be seen from the table, B. C. N. was demonstrated in 25 children in the clinical group, and no less than 20 of these were harboring the bacteria in the nose. In the control series, and in the staff, B. C. N. was isolated in one infant and one probationer, respectively. In both instances the bacteria were found on one occasion only. The remaining flora in the respiratory tract was not differentiated in detail in every case, but was only analyzed when there was some particular reason for doing so. In the main, it did not differ from the flora commonly encountered in a series of children of this type. In addition to coliform bacteria, *Staph. aureus* was the bacterium most commonly found.

Biochemical Properties of B. C. N. Strains

A total of 254 strains isolated from the feces and respiratory tract were studied from the aspect of their biochemical properties (table 3).

Table 3.

Biochemical characters of 254 strains of *Bact. coli* neapolitanum¹

V.P.	M.R.	Indol	Hemolysis	Citrate	H ₂ S	Gelatin-liquefaction	No. of strains
—	+	+	—	—	—	—	218
—	+	—	—	—	—	—	20
—	+	+	—	—	—	+	8
—	+	+	+	—	—	—	5
—	+	+	—	+	—	—	3

In all strains the V. P. reaction was negative and the methyl red test positive. With the exception of a few strains, they all also lacked the power to utilize citrate. The commonest divergence was noted in the indole test, 20 strains proving incapable of producing indole. Eight strains liquefied gelatin, and five gave a positive hemolysis test.

Antigenic Properties

All strains were agglutinated by K and O sera from the test strain. Crossed absorption tests with representative strains from the infected children showed that the B. C. N. strains isolated in these outbreaks were identical with the test strain. In British reports, motile strains are said to be uncommon. This was not found to be the case with the strains in question here; of 254 strains, 46 were motile. They were isolated from 25 of the infants and from the physician and nurse who were carriers. The H antigen was typed for 34 strains. Twenty-six belonged to type 12, 3 to type 7, 2 to type 2, 1 to type 10 and 1 to type 26. Both motile and non-motile strains were observed in the majority of the children studied over a fairly long period. An interesting feature noted was that strains with the commonest type of H antigen (12) were isolated both from infants that had become ill in hospital and from those sent in from other institutions.

¹ By reinvestigation of the properties of liquefying gelatin the results reported in this table could not be confirmed.

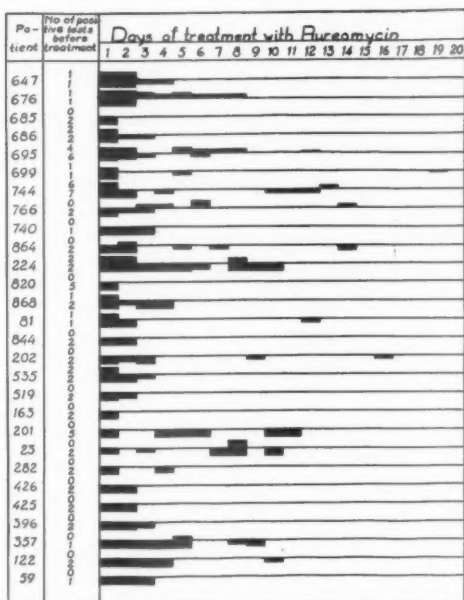


Fig. 4. Results of aureomycin treatment in the clinical group with special reference to the presence of B.C.N. The horizontal shading above the line refers to B.C.N. isolated from the respiratory tract. The shading below the line refers to B.C.N. isolated from the stools.

- Denotes a plentiful growth of B.C.N.
 ■ » a moderate growth of B.C.N.
 ■ » sparse growth (medium enriched)

Changes in the Bacterial Flora during Aureomycin Treatment

The bacteriological findings in the clinical group, with respect to the demonstration of B. C. N. during aureomycin therapy, are summarized in fig. 4. B. C. N. was, in general, found during the first few days of treatment only. In some cases, a few isolated positive tests were recorded for some time but in no case after 20 days. In these later positive tests the growth was scanty for the most part, and not infrequently it was only obtained after the

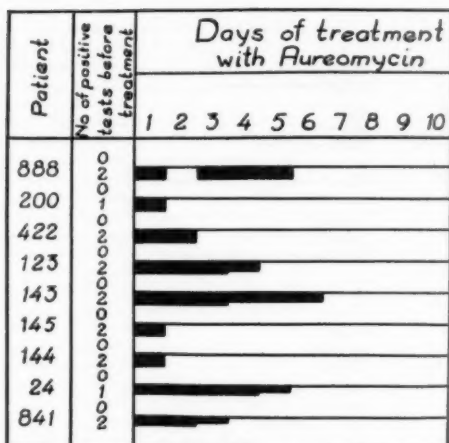


Fig. 5. Results of aureomycin treatment in healthy carriers, with special reference to the presence of B.C.N.

medium had been enriched. For the first few days after the start of the treatment the bacterial flora consisted usually of coliform bacteria not identical with B. C. N. Later on, these also disappeared, and the micro-organisms then isolated varied during different periods of treatment. During the autumn of 1949, *Monilia albicans* was the one most often encountered both in the stools and in the respiratory tract. In the second outbreak at the hospital, in particular, it was such a dominant feature that it occurred in pure culture in 11 cases. Later in the autumn, *Pseudomonas pyocyanea* was found in 7 children, and in 3 of these it formed the most dominant feature of the flora. In the spring of 1950, *B. proteus* was common, being demonstrated in 15 children. In 2 of these it occurred in greater numbers than any other micro-organism. *Staph. aureus* and enterococci, which were isolated from about one-third of the children receiving treatment, grew, in most cases, in limited numbers.

The results of the treatment in the healthy carriers are shown in fig. 5.

In five instances, B. C. N. was not found after the second day of treatment, and in no instance was it present after the sixth day

of treatment. Neither in the clinical group nor in the healthy carriers were there any signs of illness while either *Monilia albicans*, *Ps. pyocyanea* or *B. proteus* was the dominating feature of the flora. The flora soon resumed its normal character after the termination of the treatment. Only in the case of the two children in whom proteus dominated the picture was there any difficulty in reinstating the normal flora. Up to the present we have always succeeded in ridding the children of B. C. N., and follow-up examinations have proved that the results are permanent.

Agglutinins in Serum from the Patients

The question of the occurrence of agglutinins in serum against B. C. N. has been studied by several investigators, but the results have been inconsistent. In some cases, antibodies in titres of 1/32—1/64 have been demonstrated, and in one instance in a titre of up to 1/320. Usually, however, the reaction has been negative. On the whole, the results have been considered too uncertain, and the titres too low, to justify the drawing of general conclusions. Unfortunately, in our investigation, the possible occurrence of O-agglutinins was not studied until after we had begun to use aureomycin, and the clinical symptoms disappeared after a few days as the result of aureomycin treatment. In all, 45 children have been investigated up to the present. In 20 the agglutinins were demonstrated in titres of 1/40—1/80 and in a couple of cases in a titre as high as 1/160, while only 3 out of 71 controls showed titres as high as 1/40. It was also observed that, in a few children who were followed for some time during their convalescence, the agglutinins in the serum gradually disappeared entirely.

The Environment

Analysis of the air. The bacteriological analysis of the air was carried out with the aid of sedimentation plates. This study of the air was not made consistently, but was resumed every now and then when sick children were admitted to the wards. The following

findings were made. Three wards in Dept. 1 in the old hospital building were investigated consistently during the period Nov. 17th—Dec. 25th, 1949. A total of 99 plates were examined, and on no occasion was *B. C. N.* isolated. The bacteriological control of the infants cared for in these wards showed that *B. C. N.* was grown only in limited numbers in a few cases. These children had received aureomycin or were convalescing. A few *B. C. N.* were found in the nose of one child on one occasion. No nosocomial cases of gastro-enteritis occurred in these wards during this period.

In Dept. 2, the situation was quite different. The investigation time was the same as for Dept. 1, and two wards were studied. Ninety-nine plates were examined in all, and *B. C. N.* was found in 10 of them. All the positive plates were encountered during the period Nov. 25th—Dec. 15th. During this period, one infant in one ward and five in the other became ill with epidemic diarrhea and vomiting. The original source of infection was not definitely established, but *B. C. N.* was found to be present in considerable numbers in the nose of a child that was being treated in one of the wards at the time when the nosocomial infections occurred.

Later on, in the middle of January 1950, a smaller room, housing an infant in which the stools alone were found to harbor *B. C. N.*, was studied. Analysis of the air gave a negative result. On Jan. 19th a new infant was admitted to the room, and in this child *B. C. N.* was found in the respiratory tract also. The following day, analysis of the air gave a positive result, and a few days later a child in an adjoining room fell ill. In the latter room, where the child in question became a carrier of *B. C. N.* in the respiratory tract, this micro-organism was isolated from the air on three different occasions. When *B. C. N.* was no longer present in the respiratory tract the air analysis again became negative.

The air was also examined in the new isolation department, in connection with the admission to the department of a child with epidemic gastro-enteritis. Between Jan. 30th and March 10th, 1950, 35 plates in the different wards were examined, the results being negative in every plate. During this time no infections occurred in the hospital. *B. C. N.* was demonstrated in the stools only, in all children with epidemic gastro-enteritis treated in hospital dur-

ing this period. On March 27th and April 8th, 1950, two children found to be harboring B. C. N. in the respiratory tract also, in both cases in the mucous membranes of the nose, were admitted. On the day after their admission, the air analysis was positive in the wards where these children were being treated. Analysis of the air in the corridor and adjoining rooms gave a negative result and no nosocomial cases occurred. The two children that were infected in the new isolation department fell ill during the period March 19th—March 27th, and analysis of the air was unfortunately not carried out during this period. The source of infection was not established with certainty. During the period, there were infants in the same section of the department with stools containing B. C. N. in almost 100 per cent pure culture. No signs of B. C. N. were to be found in the respiratory tract, however. One of the outbreaks in one of the children's homes started when one of the carriers of B. C. N. was admitted. B. C. N. was detected in the throat, nose and feces of this child who had earlier been treated for infantile diarrhea and vomiting before being admitted to the home.

Examination of Rubber Teats, Thermometers and Milk. The rubber teats, thermometers and milk yielded entirely negative results. These examinations were carried out in connection with the second outbreak at the hospital, 52 teats, 58 samples of milk and 35 thermometers being studied. Coliform bacteria were found in one-third of them, but on no occasion was any strain identical with B. C. N. found.

Discussion

1. During the autumn of 1949 and the winter and spring of 1950, 62 children with epidemic gastro-enteritis were treated at the Sachs' Hospital for Children. In all of these children a special coli strain, termed here *Bact. coli neapolitanum* (B. C. N.), was isolated from the stools while the disease was in progress. Forty-one of the children became ill in the course of two outbreaks that occurred in the hospital during the autumn of 1949. The other children were affected in other institutions such as day nurseries, maternity hospitals and homes for post-natal care.

2. The control series consisted of children who showed no signs of epidemic gastro-enteritis while being treated at the Hospital during the same period. This group consisted of 346 children. Among them there were 12 healthy carriers of B. C. N.; only 3 of these, however, had become infected while in the hospital. The others were detected in connection with two outbreaks, one of which occurred in a day nursery and the other in a maternity hospital.

3. The Hospital Staff, comprising 151 persons, was examined regularly. The presence of B. C. N. was established in three of them. In two, a physician and a nurse, the bacteria were isolated from the stools. The nurse was suffering from mild gastro-enteritis at the time she was found to be a carrier. In the third carrier, a probationer, the bacteria were isolated from the respiratory tract.

4. The clinical picture was the same as that already described in connection with outbreaks in Anglo-Saxon countries. The dominating symptom was attacks of diarrhea of varying degrees of severity, usually in association with vomiting. All the children affected were, with one exception, less than one year old, and over one-half were under one month. A finding of particular interest was that 12 of the children were in Hospital because of prematurity. The course of the disease could be described as moderately severe or severe in two-thirds of the cases, and mild in the remainder. In conformity with the findings of British investigators, the youngest infants were often those most severely affected.

5. Penicillin, sulphonamide compounds and streptomycin were tried, but they had no specific therapeutic effect. As it was found that the B. C. N. strains were sensitive to aureomycin, treatment with this antibiotic was then started. Up to the present, 32 children have been treated. The effect was very satisfactory, even in the severe cases. After as short time as 24 hours considerable improvement was noted in many cases, and at the end of 4—5 days the signs and symptoms of the disease had entirely subsided. There have been no deaths since the introduction of aureomycin treatment. During the first outbreak in the hospital, before aureomycin treatment was introduced, several deaths occurred, and in outbreaks of this type in Britain the mortality has been reported as varying, as a rule, between 30 and 40 per cent, or even higher.

6. The result of the bacteriological investigation made in connection with the aureomycin treatment showed features of some interest. In many instances there were no longer any signs of B. C. N. after only a few day's treatment. In a few patients these strains were isolated for some time but in no case for more than 20 days. In positive samples from the latter the bacteria were usually present in small numbers and often were only detectable after the medium had been enriched. For purposes of comparison it can be mentioned that in non-treated cases, B. C. N. has, on several occasions been found as long as three months after the onset of the disease. The micro-organisms most commonly found in connection with the aureomycin therapy were *Monilia albicans*, *Ps. pyocyanea* and *B. proteus*. After the termination of treatment the flora rapidly became normal in the majority of cases.

7. It is of particular interest, especially when the method of spread is under consideration, that B. C. N. was so often present in the respiratory tract. The fact that it occurred relatively often in the nose should be stressed; this is worth noting when it is remembered that, according to recent investigations into the question of so-called dangerous carriers, those with bacteria in the nose most easily spread infection to their surroundings. LAURELL (24) has shown that coliform bacteria occur commonly in the respiratory passages of young infants and that they are often present in the nose. When they occur in the respiratory tract they behave like other bacteria in this environment, and among other things it has been proved that so-called dangerous carriers are common. It therefore seems very probable that B. C. N. is spread as an air-borne infection. The results obtained from our study of the environment provided evidence in support of this assumption. Analysis of the air revealed that B. C. N. was present in the air on two occasions at least, when the outbreaks occurred in the hospital. Bacteria were most readily demonstrated in the air when a child with B. C. N. in its respiratory passages was being treated. Investigation of other factors in the environment, such as milk, rubber teats and thermometers, were entirely negative. It seems unlikely that the infection was spread through the staff, in view of the small number of carriers.

8. The diagnostic significance to be attached to the presence of agglutinins can probably not be evaluated until after more extensive knowledge has been acquired and a closer study made of the development of agglutinins in diseased states. The investigations of ADAMSSON, LÖFGREN and MALMNÄS (41) demonstrate, however, that coli antibodies, including B. C. N., do not pass from mother to infant, and the infant is therefore totally lacking in antibodies against coliform bacteria at birth. The presence of an agglutinin would therefore apparently indicate that antibodies have been acquired after birth, and as adult pregnant women have not proved to be carriers of antibodies against B. C. N. the infants themselves must have produced them.

9. The part played by B. C. N. in epidemic gastro-enteritis is still arousing discussion. In Great Britain, the view has been advanced that the strain does not cause diseases but only occurs as a secondary feature in connection with certain forms of epidemic gastro-enteritis. An objection raised against this view is that the strain was not found in a number of outbreaks in which the clinical picture was the same as in gastro-enteritis associated with B. C. N. A co-operation between a virus and bacteria from a so-called complex infection has also been suggested.

Several observations made in the present investigation would seem to indicate, however, that B. C. N. plays a dominant part in the course of the disease. Thus, we have the fact that the rapid clinical improvement following upon the administration of aureomycin ran parallel with the disappearance of the bacteria from the stools. Another fact indicating the primary significance of these organisms was that the infections in the hospital on some occasions at least, broke out in connection with the finding of the bacteria in the air. One of the outbreaks, also, could be accounted for by the fact that a B. C. N. carrier had been admitted to the institution. It was also possible to demonstrate that B. C. N. carriers who had received treatment and been freed from the bacteria had on no occasion given rise to secondary cases. Finally, although it is not wholly convincing, the serological investigation nevertheless also showed that healthy infants do not possess antibodies against coli-

form bacteria, and to a certain extent also, agglutinins B. C. N. were demonstrated in children who had been affected.

10. Although the etiological significance of B. C. N. cannot be said to have been cleared up as yet, the diagnosing of its presence was nevertheless of great practical assistance. Thus, by establishing the presence of these bacteria it was possible to select cases suitable for aureomycin therapy, and the results of the treatment could be studied. It was also possible to know when the children were free from infection and could be returned to the various institutions. By keeping the children who were admitted to the Hospital constantly under observation it was also possible to prevent the disease from breaking out once again in general departments and therefore to prevent the occurrence of fresh hospital outbreaks. Since the establishment of control examinations in a ward for premature infants at the Sachs' Hospital for Children, for instance, no new cases have occurred within the past six months. Before such a control can be effective, however, it is necessary to have a department possessing good isolation possibilities, in which newly-admitted children can be examined and treated before being transferred to the general wards. These facilities have been available at the Sachs' Hospital for Children since the opening of the new isolation wards.

Summary

During the autumn of 1949 and the winter and spring of 1950 62 children with epidemic gastro-enteritis were treated at the Sachs' Hospital for Children. In connection with the disease a special coli strain, termed B. C. N., was isolated. Forty-one of the children became ill in connection with two outbreaks that occurred in the hospital during the autumn of 1949. The control series consisted of children who were under treatment in the Hospital at the same time but did not have diarrhea or vomiting attacks. This control group consisted of 346 children. Among these, three healthy carriers were detected. As regards the clinical picture, the dominating symptoms were loss of weight, anorexia, toxemia, diarrhea and vomiting, severe dehydration and the risk of a recurrence. Penicillin, sulphonamide compounds and streptomycin were all tried as treatment, but failed to produce any specific therapeutic effect. As it was found that the B. C. N. strains were sensitive to aureomycin, treatment with this antibiotic was instituted. Thirty-two children have been treated up to the

present. The effect was satisfactory even in very severe cases, and no deaths have occurred.

The bacteriological investigation proved that even after a few days' treatment the B. C. N. strains were no longer demonstrable. The micro-organisms most commonly occurring in connection with the aureomycin treatment were *Monilia albicans*, *Ps. pyocyanea* and *B. proteus*. In most of the cases the flora rapidly returned to normal after the treatment was terminated. So far as the aspect of the spread of the disease is concerned the most interesting observation made was that B. C. N. was very often demonstrable in the respiratory tract. Special note should be made of the fact that it was relatively often found in the nose; this is particularly noteworthy in view of recent investigations into the question of dangerous carriers of disease, in which it was shown that those with bacteria in the nose most easily spread the infection to their surroundings. It therefore seems very probable that the spread of B. C. N. may take place in the form of an air-borne infection. Analysis of the air proved, also, that on two occasions at least, in connection with the outbreaks in the Hospital, B. C. N. was present in the air. Examination of other factors in the environment, such as milk, rubber teats and thermometers, gave negative results.

The serological investigation for the purpose of demonstrating agglutination was not begun until after aureomycin treatment had been started and the clinical course of the disease thereby considerably curtailed. Agglutination was demonstrated in the serum in roughly 45 per cent of the children. In the majority of cases, however, it was present in dilutions as low as 1/40—1/80. Earlier investigations have shown that antibodies do not pass from mother to infant, and the infant therefore completely lacks antibodies against coli bacteria at birth. The occurrence of agglutination suggests, therefore, that antibodies were acquired after birth, and as adult pregnant women were not found to have antibodies against B. C. N. the infants themselves must have produced them.

The part played by B. C. N. in epidemic gastro-enteritis is still arousing discussion. Observations made in the present investigations would seem to indicate that B. C. N. plays a leading part in the course of the disease. It was noted that the rapid clinical improvement and the disappearance of the bacteria from the stools ran parallel with one another. Infections occurred in the Hospital at the same time as the bacteria were detected in the air. On no occasion did B. C. N. carriers who received treatment and were freed from the bacteria give rise to secondary cases. Finally, the serological examinations showed that healthy new-born infants do not possess antibodies against coliform bacteria, and to a certain extent, also, it was possible to demonstrate agglutinins against B. C. N. in infants that had been affected.

The diagnosing of B. C. N. proved to be of great practical significance. By establishing the presence of these bacteria it was possible to select

cases suitable for aureomycin therapy and to follow the result of the treatment. With the aid of regular control examinations it was also possible to prevent the disease from breaking out again in the Hospital. It could also be ascertained when the infants were free from infection and could be returned without risk to various institutions. All these advantages are only possible, however, at hospitals possessing an effective isolation department where newly-admitted children can be examined and come under treatment.

G. LAURELL, J. H. MAGNUSSON, E. FRISELL et B. WERNER:
Diarrhé épidémique infantile.

Pendant l'automne 1949 et l'hiver et le printemps 1950, 62 enfants atteints de dyspepsie épidémique ont été soignés à l'Hôpital pour enfants de Sachs. Chez tous ces enfants on a isolé une souche de coli appelés Bact. Coli Neapolitanum (B. C. N.). Le groupe de contrôle était composé d'enfants qui étaient soignés à l'hôpital à la même époque mais qui ne présentaient pas de signes de diarrhée épidémique. Parmi ceux-ci, on a rencontré 3 porteurs sains. Comme traitement, on a essayé l'aureomycine avec de bons résultats. Son effet fut bon, même dans les cas difficiles, et après que le traitement à l'aureomycine eut été introduit, on n'a pas enregistré de cas mortel.

La recherche bactériologique montrait que le B. C. N. disparaissait habituellement après quelques jours de traitement. Au point de vue voies de propagation de la maladie, la découverte la plus intéressante était que les bactéries pouvaient souvent être découvertes dans les voies respiratoires. Chez 25 enfants, on a isolé des bactéries dans les mucosités nasales. Plusieurs observations montrent: que les bactéries jouent un rôle central dans la maladie; qu'il y a un parallélisme entre l'amélioration clinique et le résultat des recherches bactériologiques; enfin, que les enfants, débarrassés des bactéries, n'ont pas été responsables de cas secondaires. On a trouvé des agglutinines chez 45 pour cent des enfants atteints de diarrhée infantile épidémique.

Le diagnostic a été d'une grande signification pratique. A l'aide de ce diagnostic on a choisi des cas qui s'accommodaient du traitement par l'aureomycine et on a suivi l'effet de ce traitement. Par un contrôle continu, on a empêché de nouvelles propagations de la maladie et on a pu déterminer le moment où l'enfant devenait non-contagieux et pouvait sans risque être ramené dans les maisons d'enfants etc.

G. LAURELL, J. H. MAGNUSSON, E. FRISELL und B. WERNER:
Epidemische infantile Diarrhöe.

Im Herbst 1949 sowie im Winter und Frühjahr 1950 wurden im Sachs'schen Kinderkrankenhaus 62 Kinder mit epidemischer Dyspepsie behandelt. Bei sämtlichen Kindern wurden ein spezifischer Colistamm, benannt Bact. coli neapolitanum (B. C. N.), isoliert. Das Kontrollmaterial (346 Kinder) bestand aus Kindern, die während derselben Zeit im Krankenhaus gepflegt wurden, aber keine Zeichen von epidemischer Diarrhöe aufwiesen. Unter diesen wurden drei gesunde Träger angetroffen. Bei der Behandlung wurde Aureomycin mit gutem Erfolg ausprobiert. Die Wirkung war auch in den schweren Fällen gut, und nach Beginn der Aureomycinbehandlung trat kein Todesfall ein.

Die bakteriologische Untersuchung ergab, dass die B. C. N.-Bakterien gewöhnlich schon nach ein- bis zweitägiger Behandlung verschwanden. Hinsichtlich der Verbreitungswege der Krankheit war der interessanteste Befund, dass die Bakterien oft in den Atmungswegen festgestellt werden konnten. Bei 25 Kindern wurden die Bakterien von der Nasenschleimhaut isoliert. Mehrere Beobachtungen deuten darauf hin, dass die Bakterien eine zentrale Rolle bei der Krankheit spielen: Parallelität zwischen klinischer Besserung und bakteriologischen Resultaten; bei Kindern, die frei von den Bakterien geworden waren, traten keine Sekundärfälle auf; Agglutinine wurden in gewissem Umfang (45 %) bei kranken Kindern nachgewiesen.

Die Diagnostik war von grosser praktischer Bedeutung. Mit Hilfe derselben wurden die Fälle ausgewählt, die sich für Aureomycinbehandlung eigneten, und der Effekt der Behandlung verfolgt. Durch kontinuierliche Kontrolle wurde verhindert, dass die Krankheit von neuem eingeschleppt wurde, und festgestellt, wann die Kinder ansteckungsfrei wurden und ohne Gefahr in Kinderheime usw. zurückgeschickt werden konnten.

G. LAURELL, J. H. MAGNUSSON, E. FRISELL y B. WERNER:
Diarrea epidémica infantil.

Durante el otoño de 1949 y en el invierno e primavera de 1950 pasaron por el Sachsska hospital 62 niños con diarrea epidémica. De estos casos fue aislada una cepa llamada Bact. coli neapolitanum (B. C. N.). Como material de control fueron escogidos niños que se encontraban en el hospital al mismo tiempo, pero que no presentaron síntomas de diarrea epidémica. Entre estos había 3 que aun estando sanos eran portadores de gérmenes. Se obtuvo buenos resultados haciendo un tratamiento con aureomicina. Aun en los casos severos la terapéutica con aureomicina fue eficaz y no hubo ningún caso mortal.

La investigación bacteriológica demuestra que el B. C. N. desaparece generalmente tras unos días de tratamiento. Se hizo una observación interesantísima en la investigación de la transmisión de la enfermedad, viendo que los gérmenes pueden ser hallados muchas veces en las vías respiratorias. Las bacterias fueron aisladas de la mucosa nasal en 25 niños. Otras observaciones muestran que el germen juega un papel importante en la enfermedad y la comparación entre la mejoría clínica y el examen bacteriológico demuestra que los niños libres de gérmenes no pueden dar origen a casos secundarios.

Fueron halladas aglutininas en algunos casos (45 %) de estos niños enfermos. El diagnóstico tiene una significación práctica muy grande: ayudada de los escogidos los casos que se adoptaron al tratamiento con aureomicina y en que el tratamiento fue seguido con resultados. El control riguroso ha imposibilitado que la enfermedad se introduzca y que se fije otra vez cuando los niños ya no guardan el bacilo y que ahora sin riesgo pueden ser mandados a los asilos de niños etc.

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Some Problems Concerning Mongolism in the Newborn

Diagnosis, Incidence, and Aetiology

by

JAKOB ØSTER

Mongolism is a syndrome which was separated from the group of oligophrenias by LANGDON DOWN in 1866. In an endeavour to obtain "an ethnic classification of idiots" he had been struck by the superficial resemblance of these patients to the Mongolian race and therefore coined the term "mongoloid idiots".

The present study, which is but one link in a clinico-genealogical investigation into mongolism in Denmark, deals with some of the problems arising in connection with the birth of a mongoloid baby, particularly as regards the early diagnosis, the incidence and the cause. The study is based on a series of 65 newborn mongols from the two maternity departments of the University Hospital in Copenhagen.

The diagnosis of mongolism at the age of 2—3 years is usually easy, but it may be considerably more difficult in the newborn, particularly if the babies are prematurely born. Mongolism is generally considered a developmental and growth anomaly, and according to BENDA (1946) the birth weight is below normal, whereas the birth length is said to be within the range of normal.

In certain cases the diagnosis is very easy and is, indeed, sometimes made unknowingly by the family. In other cases, however, it may be extremely difficult to make the diagnosis during the first few days of life. Although several signs may indicate mongolism one of the really pathognomonic signs may be missing and there is a risk that some cases may be overlooked and others erroneously labelled as mongols. The symptomatology of mongolism will not be dealt with further in this connection.

Despite numerous studies, the incidence among the population is not definitely known. In a given period it must depend on the birth rate and death rate among mongoloid patients during the preceding period. The latter quantity is as yet unknown, as no follow-up study has been conducted on a series from a maternity department. Only scant data have been published regarding the birth rate of mongoloid patients. JENKINS (1933) found 6 mongols among 3 818 babies born alive (0.16 % or 1 in 636) at the Presbyterian Hospital in Chicago, Obstetric Department, during the period 1926—1931 inclusive. Among 13 964 newborn babies, MALPAS (1937) found 18 (0.13 % or 1 in 776). BEIDLEMAN (1945) found 48 instances among 14 000 babies born alive (0.34 or 1 in 292) at the Boston Lying-in Hospital during the period 1931—1944. Lastly, PARKER (1950) found 32 mongols among 27 931 live born babies (0.115 % or 1 in 873) in the obstetric nurseries of the Gallinger Municipal Hospital during the period 1939—1948. Thus, the incidence among live born babies ranges from 1 in 292 to 1 in 873.

In order to elucidate the incidence of the condition and the diagnostic problems the diagnostic files and birth protocols of the two maternity departments of the University Hospital in Copenhagen from the period 1923—1948 inclusive were studied. This search yielded 57 mongols. In 3 instances the diagnosis proved incorrect on follow-up examination.

In the first case (A 1827/45) the case record stated that the patient — a girl — showed "typical mongolism". At the time of the follow-up examination she was 5 years of age and exhibited the typical picture of congenital dystrophia brevicollis. Apart from the short stature and the disabling affection of the cervical column, she was healthy and her intelligence corresponded to her age.

The second case (B 672/35) was a boy whose case record stated "appearance extremely mongoloid". At follow-up examination he was 15 years of age and was staying at his home in Jutland under the control of the Breining Asylum for Mental Defectives. He exhibited high-degree feeble-mindedness, but no stigmata of mongolism.

The third patient (B 1677/47 — a girl — had been diagnosed as a mongol despite scepticism on the part of the Pædiatric Department. At the follow-up examination she was 3 years of age and proved to be completely normal, physically as well as mentally.

In the remaining 54 cases the diagnosis may be regarded as fairly definite. In 41 instances it was confirmed elsewhere, while 13 patients died either in the maternity department or at home without having been hospitalized or seen by a specialist in the meantime.

In 2 of the 3 mistaken cases, the departments had been certain of the diagnosis. In 6 additional cases, there seems to have been some doubt, since the case records report "a suspicion of mongolism", "atypical mongolism" and the like. At the follow-up examination all 6 patients proved to be affected with typical mongolism — a fact which illustrates the finding that "the typical mongoloid appearance" is accentuated during the first years of life.

From another series of about 1000 mongols, 11 were reported to have been born at the maternity departments of the University Hospital during the period 1923—1948, without the case records containing any remarks about mongolism.

Thus, among 68 infants born during the period 1923—1948 inclusive for whom a diagnosis of mongolism was made at birth or later, there was a total of 14 erroneously diagnosed or non-diagnosed cases (about 21 %). When considering also the high mortality among these patients during the first years of life there is reason to presume that the actual number of non-diagnosed cases is greater.

This leaves a total of 65 cases of definite mongolism, diagnosed during the period 1923—1948. Table 1 sets out their distribution among the two maternity departments and the years of birth. A calculation on the basis of the figures in Table 1 shows that among the 84 072 babies born alive in the two departments in the course of the 26-year period, there were 65 mongols, i.e. $0.77 \frac{\%}{100}$ or 1 in 1 293. The same values for each department separately and for the period 1938—1948 are given in Table 2. It is interesting to note that during the period 1938—1948 there were 32 mongols among 20 391 babies born alive in Dept. B, i.e. $1.57 \frac{\%}{100}$ or 1 in 637. Owing to the previously mentioned difficulties connected with the diagnosis of mongolism at birth, the last-mentioned figure is probably closer to the true incidence of mongolism, with the

Table 1.

The distribution of sixty-five mongols according to year of birth, maternity department, and sex.

Year	Department A		Department B	
	Number of mongols	Number of live born children	Number of mongols	Number of live born children
1923		1 583		1 675
1924		1 492		1 445
1925	♂ 1	1 410		1 389
1926		1 411		1 454
1927		1 457	♀ 1	1 436
1928		1 413		1 408
1929		1 408		1 408
1930		1 410	♀ 1	1 500
1931	♂♂♂ 3	1 482	♂♀ 2	1 454
1932	♂♀♀ 3	1 412		1 525
1933		1 449	♀ 1	1 519
1934		1 300		1 537
1935		1 354	♂♂ 2	1 542
1936	♂ 1	1 452	♂ 1	1 636
1937		1 598		1 725
1938	♂ 1	1 638	♀ 1	1 733
1939	♀♀ 2	1 543	♀ 1	1 639
1940	♂♀ 2	1 770	♂♂ 1	1 808
1941	♂♀ 2	1 659	♀♀ 2	1 756
1942	♀ 1	1 755	♂♂ 2	1 866
1943		1 858	♂♂♀ 3	1 975
1944	♂ 1	1 914	♂♂♂♀ 4	1 844
1945	♂♂ 2	1 982	♂♂♀♀♀♀ 6	1 863
1946	♂♀♀ 3	1 898	♂♀♀ 3	2 047
1947	♂♂ 2	1 691	♂♂♀♀♀ 5	2 015
1948	♀ 1	1 689	♂♀♀ 3	1 845
	25	41 028	40	43 044

reservation that even this must be a minimum value. Lastly, it must be borne in mind that this may not indicate the true incidence of mongolism among the population, since the series is derived from a hospital which receives almost exclusively un-

Table 2.

	Dept.	Number of live born children	Number of mongols	Number of mongols per 1 000 live- born children	1 mongol per number of live born children
1923-48	A	41 028	25	0.61	1 : 1 641
	B	43 044	40	0.93	1 : 1 075
	A & B	84 072	65	0.77	1 : 1 293
1938-48	A	19 397	17	0.82	1 : 1 141
	B	20 391	32	1.57	1 : 637
	A & B	39 788	49	1.23	1 : 812

married mothers (often tantamount to young primiparae) and married women with a history of abnormal pregnancies and deliveries.

Several previous workers have reported a higher incidence of mongolism among boys than among girls — mainly on the basis of institutional cases. In this series of 65 patients, 35 were boys (53.85 %), whereas 52.15 % of all the babies born in the departments during the period in question (89 859) were boys.

The average birth weight of the 65 patients was 2 774 g and the length 48.1 cm. In this connection it must be pointed out that 36 (55.4 %) were premature (1—8 weeks). The fate of 64 children is known. In one case it proved impossible to identify the mother and find the child, since the mother, who was unmarried, had been admitted without having to state her name. The follow-up examination took place 2 years after the birth of the last child included in the series. At that time 44 had died (67.7 %), 32 within the first year of life (49.2 %) and 21 even within the first 3 months. Five died during the second year of life, 2 during the third, 3 during the fourth, 1 during the fifth year, and 1 at the age of 20. The majority had died in Children's Departments, in most cases from intercurrent infections, often associated with congenital cardiac malformation. From birth mongols show great susceptibility and highly reduced resistance to infections. Among the 20 survivors, 10 were staying at their homes and 10 were in institutions for mental defectives. They ranged in age from 2 to 19 years.

The aetiology has been the subject of numerous investigations most of which show that the incidence of mongolism increases with the mother's age and that the average age of mothers giving birth to mongoloid babies is higher than the average age of child-bearing women (BEALL & STANTON, 1945). Previously, it was believed that these children were the last of a large family, but PENROSE (1934) has shown beyond doubt that the maternal age and not the number of siblings is significant. Many workers have directed their attention to the mother's health before and during the pregnancy, trying to find the cause of the general pathological development of the foetus (endocrine disturbances, generalized diseases such as syphilis, tuberculosis, or German measles, insufficiency of the uterine mucosa, uterine bleeding and threatening abortion, abortion and curettage; abortives, contraceptives etc.). For the present, however, it must be admitted that it is not known how the maternal age is related to the developmental inhibition which leads to mongolism.

Twin studies have confirmed with only a few exceptions that in monozygotic twins both are mongols, whereas only one of a pair of heterozygotic twins is a mongol. This finding prompts an investigation into the influence of hereditary factors.

Only 44.3 % of the mothers in this series (88 783) were married, but among the mothers of the 65 mongols 41 (63.1 %) were married. As apparent from Table 3, their average age was higher than that of the unmarried mothers. The average age for all 65 mothers was 31.2 years. The average age for the other patients admitted to the departments is unknown.

Table 3.

Mothers	Number of mongols in Dept. A	Age of mothers in Dept. A	Number of mongols in Dept. B	Age of mothers in Dept. B	Total number of mongols in Depts. A & B	Age of mothers in Depts. A & B
married ..	17	32.8	24	33.6	41	33.2
unmarried	8	27.1	16	27.9	24	27.7
total	25	31.0	40	31.3	65	31.2

In 24 cases the mongol was the result of the first pregnancy (36.2 %) and only in 3 cases from a pregnancy later than the fifth. Among all the mothers 59.5 % were primigravidae.

Judging from those case records which offer sufficient data

(the majority), the menstruation appears to have been normal in all cases. The menarche had set in between 12 and 16 years of age, and signs of approaching menopause had not been noted in any case at the time of conception. However, a 40-year-old patient reported menstrual periods at fortnightly intervals during the past 3 years, "since her last pregnancy".

As regards the past history, 10 had had venereal diseases (3 gonorrhoea, 1 syphilis), and 5 salpingitis or genital abnormalities (4 years previously one mother had been treated by perturbation because of sterility, and 8 years previously another one had undergone surgical correction of malposition of the uterus). In 5 instances, all of salpingitis, the interval from the disease until conception was less than one year. Two mothers had suffered from non-toxic goitre and two from pulmonary tuberculosis (which was still active during pregnancy in one of the cases). One mother had suffered from tetany for 3 years. None of the remaining mothers had a history of serious lesions.

In 13 instances, the mother had miscarried previously, one twice, another one four times, and the remaining 11 only once. The miscarriage had occurred more than one year prior to the conception of the mongoloid baby except in two cases in which the interval was only 7 and 3 months respectively. The last mother reported a history of syphilis and had been treated with neoarsphenamine and bismuth during pregnancy, but exhibited no signs of syphilis at the time of delivery.

During pregnancy 38 mothers had more or less severe complaints, but it is difficult to estimate the gravity of the complaints on the basis of the data in the case records. In 9 instances vaginal bleeding occurred, usually in the form of negligible bleeding one month after the last normal menstrual period. In one case the bleeding proved to come from an erosion of the uterine cervix; in another case in which the bleeding continued during every day of the pregnancy, the cause could not be demonstrated. Neither in this nor in the other cases did the placenta offer any explanation of the bleeding. In one instance exploratory laparotomy was done in the third month of pregnancy because of a suspicion of extrauterine pregnancy, and a bicornate uterus with a 2-month-old foetus in the right horn was found; the remainder of the pregnancy was uneventful. Among other serious complications during pregnancy it is worth mentioning that one patient had a syphilitic infection in the 2nd or 3rd month and received neoarsphenamine and bismuth; another patient had parametritis at the beginning of pregnancy, and a third patient had active pulmonary tuberculosis and was treated by artificial pneumothorax throughout the period of pregnancy.

The maternal Wassermann reaction had been tested in 20 cases and

found to be negative in all, as was also the case in the patients with a past history of syphilis.

In 59 instances the delivery was described as normal. In one case Caesarean section was performed to deliver a living child. Two were forceps deliveries because of faint heart sounds, and in two instances the delivery was protracted because of a secondary reduction in the uterine contractions. Finally, in one case the delivery was induced prematurely, because the mother, who has been receiving antisyphilitic treatment during pregnancy, had developed proteinuria and hypertension.

One mother died from puerperal sepsis; the mother who underwent Caesarean section developed pulmonary infarction and phlebitis of the leg, but was discharged in good health. In the remaining 63 cases the puerperium was uneventful.

The case records contain a detailed description of the placenta. In 11 cases it was somewhat "loose and multilobed" and in 12 instances the membranes were ragged or ruptured. In 10 cases white infarcts were noted, but they were few in number and occupied only a small part of the placenta. Four had a velamentous placenta. All these changes must be called slight, and more severe changes occurred in only one case: "The placenta is multilobed. Rupture of the membranes about 3 cm from the edge. On a level with this site there is a depressed area, 5 × 10 cm, covered by old blood clots which are fairly easy to detach". This patient had had no complaints during pregnancy, particularly no vaginal bleeding.

Since the present series is small and, as mentioned above, not representative, and since the mothers were not questioned with a view to elucidating the possible aetiological factors of mongolism, further comments must await the results of a recently concluded investigation comprising a large non-selected series. In addition to dealing with the clinical aspects, this investigation will presumably contribute to solving some of the pathogenetic and aetiological problems mentioned above.

Summary

As a link in a major investigation into mongolism in Denmark, 65 mongols were found among 84 072 live born babies (0.77 % or 1 in 1 293) in the two maternity departments of the University Hospital in Copen-

hagen during the period 1923—1948 inclusive. During the period 1938—1948 inclusive one of the departments had 32 cases among 20 391 live born babies (1.57 ‰ or 1 in 637). The latter figure is considered to be closer to the true incidence at birth.

The difficulties connected with early diagnosis are mentioned. In about 21 % of the cases the condition was either not diagnosed or was diagnosed erroneously immediately after birth.

A follow-up examination was conducted 2 years after the birth of the last child included in the series. At that time 44 (66.7 %) had died, 32 (49.2 %) of them during the first year of life.

The presumed ætiology of the condition is briefly mentioned, and the health of the mothers before and during pregnancy is described, but no conclusions are drawn, since the series is rather small and not representative.

J. ØSTER: Quelques problèmes concernant le mongolisme chez les nouveaux nés. Diagnostic, fréquence et étiologie.

Parmi les recherches faites au Danemark sur le mongolisme, lors d'une investigation importante, l'auteur a trouvé 65 mongoloïdes parmi 84 072 bébés, nés vivants (0,77 ‰ ou 1 pour 1 293), dans les deux maternités de l'Hôpital Universitaire de Copenhague pendant la période comprise entre 1923 et 1948 inclusivement. De 1938 à 1948 inclus, un de ces services a eu 32 cas parmi 20 391 enfants nés vivants (1,57 ‰ ou 1 pour 637). On peut considérer ce dernier chiffre comme plus près de la véritable fréquence à la naissance.

L'auteur rapporte aussi les difficultés liées au diagnostic précoce. Dans 21 % des cas, le mongolisme était ou non diagnostiqué ou était faussement diagnostiqué immédiatement après la naissance.

Un examen ultérieur fut fait 2 ans après la naissance du dernier enfant inclus dans les listes. A ce moment 44 (soit 67,7 %) étaient morts et parmi eux 23 (49,2 %) pendant leur première année d'existence.

L'auteur mentionne aussi brièvement, l'étiologie présumée du mongolisme. Il décrit l'état de santé de la mère avant et pendant la grossesse mais sans les commenter aucunement, étant donné le nombre plutôt petit et peu représentatif des cas de la série.

J. ØSTER: Einige Probleme betreffend Mongolismus bei Neugeborenen. Diagnose, Frequenz und Ätiologie.

Als Teilergebnis einer grösseren Untersuchung über Mongolismus in Dänemark fand der Verfasser in den beiden Entbindungsabteilungen der Universitätsklinik in Kopenhagen während des Zeitraums 1923—1948 inkl. unter 84 072 lebendgeborenen Kindern 65 Mongoloide (0,77 ‰ oder

1 von 1 293). In der Zeit 1918—1948 inkl. hatte eine der Abteilungen 32 Fälle unter 20 391 Lebendgeborenen (1.57 ‰ oder 1 von 637). Die letztere Ziffer dürfte der wirklichen Frequenz bei der Geburt näherkommen.

Die Schwierigkeiten der Frühdiagnose werden erwähnt. In etwa 21 % der Fälle wurde der Zustand unmittelbar nach der Geburt entweder nicht oder unrichtig diagnostiziert.

Zwei Jahre nach der Geburt des letzten in den Serien enthaltenen Kindes wurde eine Nachuntersuchung vorgenommen. Zu dieser Zeit waren 44 (67.7 %) gestorben, davon 32 (49.2 %) während des ersten Lebensjahres.

Die vermutete Ätiologie der Erscheinung wird kurz erwähnt und der Gesundheitszustand der Mütter vor und während der Schwangerschaft beschrieben, aber ohne Kommentar, weil die Serie ziemlich klein und nicht repräsentativ ist.

J. OSTER: Algunos problemas que ocurren en el mongolismo de los niños recién nacidos. La diagnóstico, ocurrencia y etiología.

El autor, en una gran investigación sobre el mongolismo en Dinamarca, descubrió como un punto, la existencia de 65 niños mongoloides entre 84 072 niños nacidos vivos (0.77 ‰ ó 1 en 1293) en los dos departamentos de maternidad en el hospital universitario, durante los años 1923—1948 inclusivos. Durante el período entre 1938—1948 y durante el año 1948 uno de los departamentos tenía 32 casos entre 20 391 niños vivos (1.57 ‰ ó 1 en 637). La última figura es considerada como la más aproximada a la ocurrencia al nacimiento.

Las dificultades de la diagnosis temprano son tratadas, en aproximadamente 21 % de los casos la condición no fue diagnosticada ó fue interpretada erróneamente inmediatamente después del nacimiento.

Para ver la secuela, una examinación fue hecha 2 años después del nacimiento del último niño incluido en la serie. A este tiempo 44 (67.7 %) se habían muerto, 32 (49.2 %) en el primer año de vida.

Se trata un poco de la etiología posible, y porque la serie es pequeña y por lo tanto no representativa del caso verdadero, se limita a describir y no a comentar sobre la salud de las madres antes y durante el período de gestación.

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Fibrocystic Disease of the Pancreas, a Disorder of the Autonomic Nervous System

by

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Cystic fibrosis of the pancreas has been delineated by ANDERSEN into three groups. The first group includes patients who die during the first week or two of life because of meconium ileus. The second group includes these patients who die between the ages of 1—2 weeks and 6 months of purulent bronchitis, bronchiectasis or bronchopneumonia. Most of these cases also present feeding problems, the essential features of which are failure to gain weight on an adequate diet and the presence of foul bulky stools. The third group includes children from 6 months of age up to puberty who have symptoms of celiac disease. These patients also suffer from chronic bronchitis.

The histologic appearance of the pancreas varies considerably, apparently depending on the developmental stage of the disease. In the advanced cases the ducts and acini are dilated and contain coagulated, inspissated secretion. The secreted material occasionally has a laminated appearance and is acidophilic. In some ducts it stains as mucus and occasionally as fibrin. The cells of the epithelial lining are flattened. There is atrophy of the acinar parenchyma and increase of interacinar and interlobar connective tissue. In the earliest stage of the disease the acini and ducts are dilated only slightly and only slight increase in the interacinar connective tissue is present.

Inspissation of the secretion and distention of the glands has been observed, however, also in organs other than the pancreas. More or less regularly the mucosal glands of the small intestine, the Brunner's glands, the salivary glands and the mucous glands

of the cystic duct are involved. In cases belonging to groups 2 and 3 the bronchial lumina are filled with mucopurulent exudate and the epithelium of the bronchi is often composed of more cell layers than usual. Squamous metaplasia and keratinization of the superficial layers has been observed.

Inspissation of the secretion of the cystic duct prevents the flow of bile into the gallbladder, which contains only a small amount of translucent, gray mucus. In a few cases biliary and even portal cirrhosis is present. More frequent is fatty metamorphosis of the liver. Hemosiderin is almost invariably present in the liver and in the spleen. Calcium salts are occasionally found as casts in the distal tubules of the kidneys, and generalized osteoporosis has been found in some cases. The significance of these findings is unknown, but they may indicate some disturbance in the calcium metabolism. In cases belonging to group 1 the lower part of the intestine is plugged by thick, putty-like meconium. The intestine above is more or less dilated. Malformations in organs other than pancreas are present in many cases. In several cases the islands of Langerhans retain their connections with adjacent ducts but appear normal in other respects.

Fibrocystic disease has a tendency to occur in more than one member of a family.

The underlying cause of the disease is not definitely known. The presence of the condition in the newborn and its early development in infants, the familial incidence and the common association of the disease with other malformations favours the hypothesis that it is of congenital origin. Several explanations for its pathogenesis have been given but they can be grouped into two main theories. The first of these theories was advanced as early as 1905 by LANDSTEINER, who first described the disease and believed a pancreatic disturbance to be the primary cause resulting in hyperfunction of the secretory mechanism followed by meconiumileus or the celiac syndrome. More recent authors have explained the keratinization of the epithelium in the lungs and trachea as due to a vitamin-A deficiency following the intestinal insufficiency. That vitamin-A deficiency may be present has been shown beyond doubt by laboratory methods.

The second theory advocated by FARBER, ZUELZER and NEWTON and others, represents the disease as a general disturbance of the secretion of mucus. The keratinization in the respiratory tract is not caused by vitamin-A deficiency but is a sequence of inflammatory processes secondary to the glandular disorder. Those subscribing to this theory emphasize that the keratinization is localized only to the respiratory tract and that it occurs only after a long standing bronchitis. The underlying cause, according to FARBER, is a disturbance of the parasympathic innervation or an autonomic imbalance in the nervous control of the secretion. He even produced the histologic picture of inspissation of secretion in the acini and small ducts of the pancreas of kittens by the administration of pilocarpin and acetylcholin, thus stimulating the cholinergic system.

Recently the present writer has had the opportunity to do the histological examination on two cases of fibrocystic disease of the pancreas. The first case has been reported from clinical point of view by EHRENPREIS.

Case 1 was a girl 7 weeks of age at death who was admitted because of vomiting and ileus.

At operation the terminal ileum, the colon and the rectum showed contraction, the main part of the ileum and the entire jejunum being distended. At autopsy, unfortunately only the organs of the abdominal cavity were preserved.

Histological examination: In the terminal, contracted part of the ileum and in the colon and rectum, ganglion cells were totally absent. The nerve fibers of the myenteric plexus were normal. No Paneth cells were observed in any part of the small intestine. The mucosal glands were not visibly distended but contained round concretions of inspissated secretion, the central parts of which stained like calcium salts when appropriate stains were used (fig. 1). The intestinal content included many concretions of this kind.

The ganglions of the stomach were of normal appearance, but none could be seen in the small part of *oesophagus* preserved together with the stomach.

The liver showed an enormous hemosiderosis with the pigment localized to the parenchyma cells and the Kupffer cells, mainly to the latter. The periphery of the acini was more pigmented than the central parts. An insignificant fatty infiltration was seen in some of the paren-

chyma cells, especially in the periphery of the acini. There was no increase of connective tissue and no distention of the bile ducts.

The mucosa of the gallbladder was lined by high mucous-producing epithelial cells. No bile pigment was present. The glands of the neck of the gallbladder were distended by inspissated mucus (fig. 2) and mucus filled the lumen of the *cystic duct*. No abnormalities of the common or hepatic ducts were noted.

Pancreas showed, as in other early cases, only minor lesions. There was only a slight increase of connective tissue and the large ducts were not dilated; but the lumina of the small ducts and the acini contained acidophilic, inspissated, partly-lamellated secretion and were dilated. The inspissated secretion was absent in some lobules. Small areas of necrosis of pancreatic parenchyma were seen in a few places.

The *spleen* contained great amounts of haemosiderin.

The *renal* parenchyma showed casts in the distal tubules containing calcium salts (v. Kossa) and hemosiderin (Prussian-Blue reaction) but not hemoglobin (Lison-Dunn). A few epithelial cells in the proximal tubules showed so-called "hyaline droplet degeneration". The *pelvic mucosa* was not thickened and the cells maintained their transitional character.

The fatty tissue around the *adrenal glands* enclosed numerous aberrant islands of adrenal cortical gland tissue, the cells of which differed from the normal by being larger and more eosinophilic. Small hemorrhages were noted in the adrenal medullae.

New findings in this case were the absence of Paneth cells and agenesis of the ganglion cells in a great part of the intestine, in combination with meconium ileus and cystic fibrosis of the pancreas.

Case 2 was a girl 20 months of age at death. The patient had three siblings, of which one (a girl) died suddenly at the age of four weeks and one (a boy) at the age of four months. The latter had suffered from dystrophy, dyspepsia and chronic bronchitis, and death was attributed to a lung abscess.

Up to the time she was 4 1/2 months of age the patient suffered from loose stools but was otherwise healthy. At this time she fell suddenly ill with high temperature and general convulsions lasting one hour; similar episodes occurred during the next several days and lasted 15–45 minutes. After that her condition improved but she began to cough and show dyspeptic symptoms with bulky, foul smelling, diarrheic stools. She vomited rather frequently. Periods of comparative health alternated with periods characterized by more or less severe symptoms of infection of the respiratory tract. The gastrointestinal symptoms were mild but the stools were all the time foul smelling. She died 15 1/2 months after the onset of symptoms, the immediate cause of death being bronchitis.

Autopsy showed a yellow-green muco-purulent exudate in the bronchi and trachea. The pancreas weighed 8 g and displayed a rather striking lobulated appearance but no cysts.

Histological examination: The trachea was filled with mucus containing numerous leukocytes. Its lining consisted of normal pseudo-stratified ciliated columnar epithelium. In some places the epithelium had changed to true stratified epithelium and had lost the cilia but showed no keratinization. The mucosal glands were greatly distended, lined with flattened epithelium and distended by inspissated mucus (fig. 3).

The bronchial ramifications were filled with disintegrating polymorphonuclear leukocytes mixed in the main bronchi, but not in the intra-pulmonary bronchi, with mucus. The intra-pulmonary bronchi were lined with columnar ciliated epithelium (fig. 4). No goblet cells were seen except for a few in the main bronchi. The mucosal glands, which normally are found as far out as the cartilage extends, were distended by inspissated mucus (fig. 7). The bronchial walls showed a sub-epithelial inflammatory cellular infiltration mainly of round cells. No eosinophilic cells were present. Ganglion cells were observed in both the trachea and the main bronchi. There were small areas of peri-bronchial alveoli filled with purulent exudate.

The parenchyma of the *pancreas* had been largely replaced by connective tissue and only a few dilated ducts and acini were present. The cells of the epithelial lining were flattened and the lumina contained varying amounts of laminated material staining like mucus and occasionally like fibrin. The islands of Langerhans were isolated in the connective tissue but showed no abnormalities.

The *liver* showed a fairly severe fatty metamorphosis, mainly in the form of small droplets in the parenchyma cells distributed evenly over the entire acinus. A few liver cells, especially in the periphery of the acinus, showed hemosiderin pigment.

In the *esophagus, stomach* and *intestine* no abnormalities were observed except that the Brunner glands were much distended and lined with flattened epithelium (fig. 6). They did not, however, contain any inspissated secretion.

The *spleen* was overloaded with blood and a few endothelial cells contained iron pigment.

In the *kidneys* no abnormalities were noted.

Before discussing these two cases we should comment briefly on present knowledge concerning the disorders called *achalasia* and, especially, *Hirschsprung's disease*.

During the years 1948—49, several investigations were published which helped greatly toward an understanding of the pathogenesis of this disease. On the basis of large materials, ZUELZER and WILSON, WHITEHOUSE and KERNOHAN, BODIAN et al. showed that ganglion cells are absent in the plexuses of AUERBACH and MEISSNER in the contracted part of the intestine, i.e. principally the rectum, but are present in the dilated part. The agenesis of the parasympathic relays explains the lacking of the propulsive function in the contracted portion, and the contraction itself is supposedly due to sympathetic action unmitigated by parasympathic counteraction. These findings were not new (DALLA VALLE 1920 among others) but the cases published earlier were few and were not used as a basis for the development of this theory.

According to WHITEHOUSE and KERNOHAN ganglion cells are absent in the rectum in 100 % of the cases but are absent in the distal sigmoid in only 60 % and in the proximal sigmoid in 20 %. The abnormality thus has its starting point at varying distances from the anus.

It is tempting to try to explain even other achaliasias such as those of the esophagus and stomach and megaloureter etc. as due to a similar agenesis, especially since they often occur combined. As a matter of fact, ETZEL showed as early as 1937 that 9 of 11 cases of megaloesophagus lacked ganglion cells in throughout the entire length of the esophagus. He even pointed out that megaloesophagus in more than half of the cases was combined with pylorospasm, megaloureter, distended bladder and hydronephrosis. ETZEL believed, however, that the absence of ganglion cells was due to an inflammatory process — a theory that seems questionable.

In the first of my cases, an agenesis of the ganglion cells was noted in a much greater part of the intestine than in Hirschsprung's disease. The case is not unique. A similar case is included in ZUELZER and WILSON's material (case 9) and one is published by PERROT and DANON. In the latter case, however, ganglion cells were present in the colon descendens, flexura sigmoidea and the rectum. The pancreas was not examined in these cases.

FIBROCYSTIC DISEASE OF THE PANCREAS

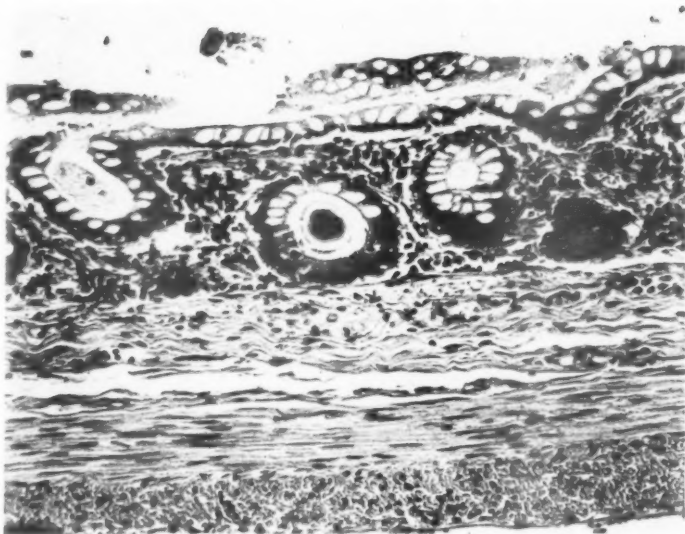


Fig. 1. Case 1. Inspissated secretion in the mucosal glands of the small intestine.

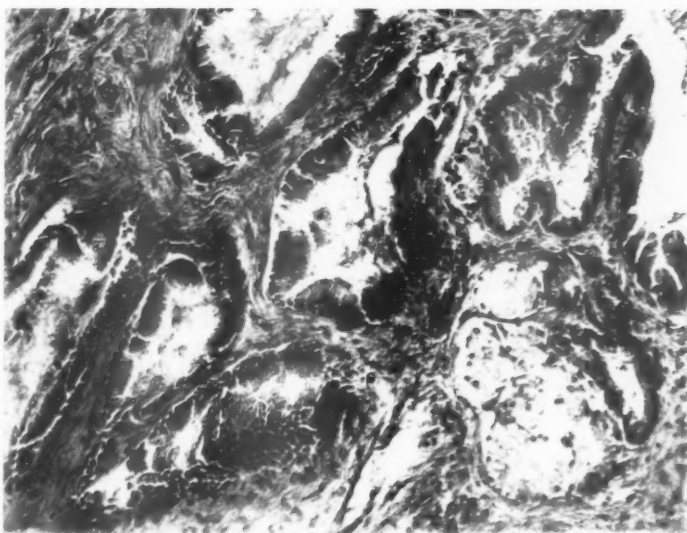


Fig. 2. Case 1. Inspissated mucus in the distended glands of the neck of the gallbladder.

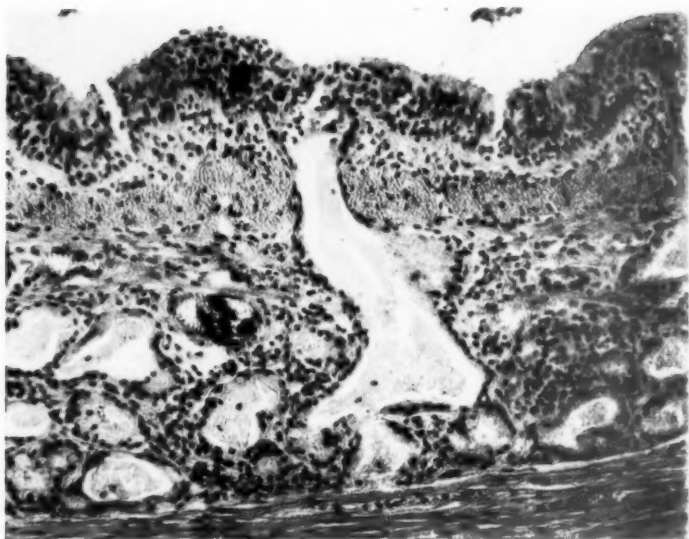


Fig. 3. Case 2. Mucosal glands in the trachea distended by inspissated mucus.

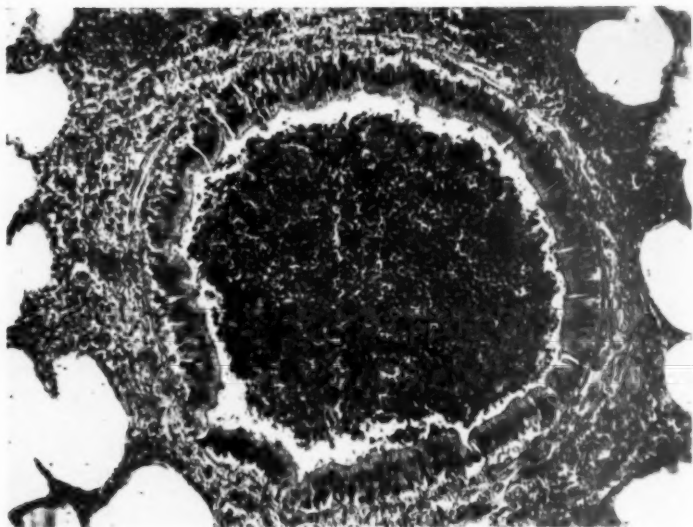


Fig. 4. Case 2. Intra-pulmonary bronchus lined with columnar ciliated epithelium and filled with disintegrating leukocytes. No goblet cells.

FIBROCYSTIC DISEASE OF THE PANCREAS

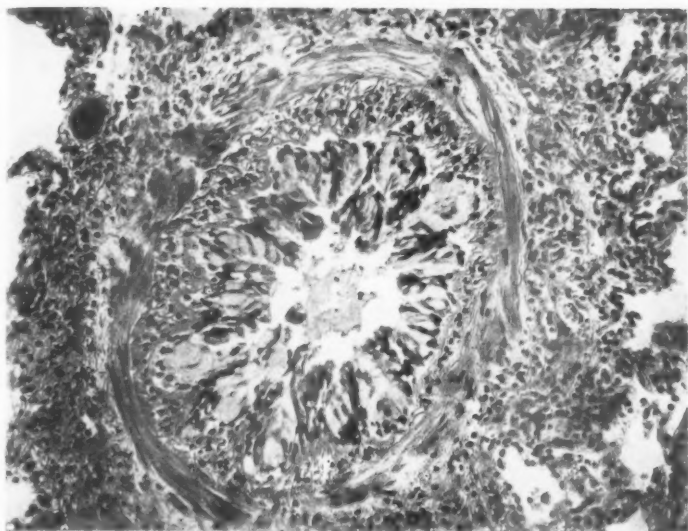


Fig. 5. Intrapulmonary bronchus from a case of asthma. The mucosal lining consists entirely of goblet cells. The subepithelial layer is infiltrated by eosinophiles and the smooth-muscle is hypertrophic and thickened.

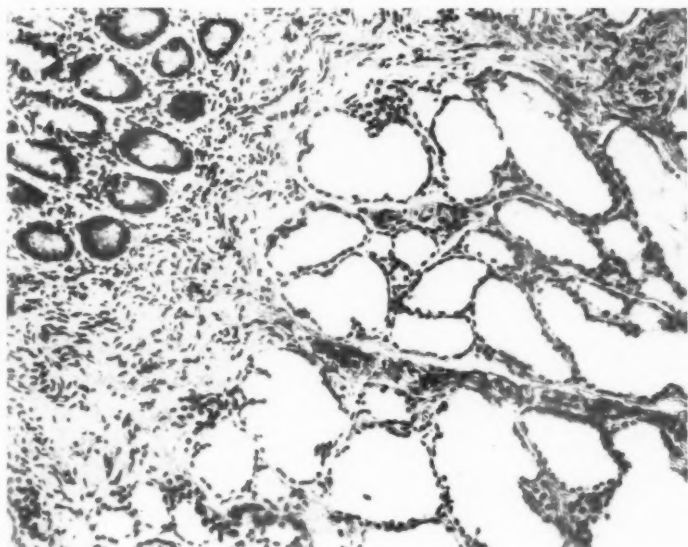


Fig. 6. Case 2. Distended Brunner glands lined with flattened epithelium.



Fig. 7. Case 2. Mucosal glands in a main bronchus distended by inspissated mucus. No goblet cells in the epithelial lining of the mucosa.

It is highly probable that all the cases of ANDERSEN's group 1 were of the same kind, judging from the gross appearance described in the autopsy reports and from the fact that many of them were combined with other achaliasias.

The above-mentioned facts lend strong support to FARBER's theory.

The second case is interesting in many ways. There is no absence of ganglion cells but only the other signs of a parasympathic disorder as described in earlier cases. But what had not been noted in earlier cases were the peculiar changes in the mucosa of the respiratory tract. The increased mucus production was due to a hyperfunction or dysfunction of the mucous glands, but there was no conversion of the columnar cells to goblet cells. The picture thus differs greatly from that in asthma (fig. 5), a disease in which the parasympathic system is believed to be in an overstimulated state. The facts seem to indicate that the disorder of the parasympathic system in fibrocystic disease of the pancreas is not a hyperfunction but a dysfunction, contrary to FARBER's conception as based on his experiments. This is in better agreement with the findings of an agenesis of ganglion cells in at least some cases. Even the abnormal inspissated appearance of the secretion supports such a conclusion.

All other symptoms, e.g. the hemosiderosis, the osteoporosis, the fatty metamorphosis of the liver, the alimentary disorders etc., can be explained as secondary.

Summary

The author describes two cases of cystic fibrosis of the pancreas. The first case, that of a girl seven weeks of age at death, showed agenesis of the ganglion cells in the distal ileum and in the entire colon and rectum. No Paneth cells were present in the small intestine. In the second case, that of a girl 20 months of age at death, no abnormalities of the sympathetic nervous system could be found on microscopic examination. As in some previously described cases, the mucous glands of the respiratory tract in this second case were distended and contained inspissated secretion, but goblet cells were practically absent. Consequently, the microscopic appearance of the lungs was quite dissimilar to that in asthma, a disease in

which the parasympathetic nervous system is believed to be over-stimulated. The author draws the conclusion that both of his cases strongly support FARBER's theory that the basic disorder of cystic fibrosis of the pancreas is an imbalance of the autonomic nervous system. He believes, however, that the cases do not tally with FARBER's conception of the disorder as hyperfunction of the parasympathetic nervous system but that they suggest it to be a dysfunction or a hypofunction of this system.

H. BERGSTRAND: *Maladie fibrokystique du pancréas, desordre du système nerveux autonome.*

L'auteur décrit 2 cas de fibrose kystique du pancréas. Le 1er cas, celui d'une fillette morte à 7 semaines, montre une agénésie des cellules ganglionnaires dans la partie distale de l'iléon et dans le colon et le rectum sur toute leur longueur. On ne trouva aucunes cellules de Paneth dans l'intestin grêle. Dans le second cas, celui d'une fillette morte à 20 mois, on ne trouva aucune anomalie du système nerveux sympathique à l'examen microscopique. De même que dans quelques cas décrits antérieurement, les glandes muqueuses du tractus respiratoire, dans le second cas, étaient distendues et contenaient une sécrétion sèche, mais les cellules de goblet étaient pratiquement absentes. Consécutivement, l'examen microscopique des poumons était très différent de celui de l'asthme, maladie dans laquelle on suppose que le système nerveux parasympathique est trop sollicité. L'auteur en conclue que ces deux cas confirment la théorie de Farber, selon laquelle le désordre de base de la fibrose kystique du pancréas est un déséquilibre du système nerveux autonome. Il pense cependant, que ces cas ne sont pas en accord avec la conception de Farber selon laquelle le désordre est un hyperfonctionnement du système nerveux parasympathique, mais qu'au contraire ils suggèrent que se serait une dysfonctionnement ou une hypofonctionnement de ce système.

H. BERGSTRAND: *Fibrozystische Pankreasfibrose, eine Störung des autonomen Nervensystems.*

Der Verfasser beschreibt zwei Fälle von zystischer Fibrose des Pankreas. Der erste Fall, ein beim Tode sieben Wochen altes Mädchen, zeigte Agenesie der Ganglienzellen im distalen Ileum sowie im ganzen Colon und Rectum. Im Dünndarm fanden sich keine Panethschen Zellen. Im zweiten Fall, ein beim Tode 20 Monate altes Mädchen, konnten bei mikroskopischer Untersuchung keine Anomalien des sym-

pathischen Nervensystems festgestellt werden. Wie in einigen früher beschriebenen Fällen waren die Schleimdrüsen des Atmungssystems in diesem zweiten Fall erweitert und enthielten verdicktes Sekret, aber Becherzellen waren praktisch genommen nicht vorhanden. Infolgedessen war das mikroskopische Aussehen der Lunge ganz verschieden von dem bei Asthma, einer Krankheit, bei der, wie man annimmt, das parasympathische Nervensystem überreizt ist. Der Verfasser zieht den Schluss, dass seine beiden Fälle eine starke Stütze für Farbers Theorie sind, derzufolge die Grundstörung bei zystischer Fibrose des Pankreas mangelndes Gleichgewicht des autonomen Nervensystems ist. Er glaubt indes, dass die Fälle nicht mit Farbers Auffassung der Störung als einer Hyperfunktion des parasympathischen Nervensystems übereinstimmen, sondern darauf hindeuten, dass sie in einer Dysfunktion oder einer Hypofunktion dieses Systems besteht.

H. BERGSTRAND: *La fibrosis quística del páncreas como trastorno del sistema nervioso autónomo.*

El autor comunica dos casos de fibrosis quística del páncreas. El primero de ellos se trataba de una niña que tenía 7 semanas de edad cuando murió, en el examen anatómo-patológico se encontró una agenesia de las células ganglionares de la porción distal del íleon y en todo el colon y recto. No había células de Paneth en el intestino delgado. En el segundo caso correspondiente a una niña que murió a los 20 meses de edad el examen histológico no mostró ninguna alteración del sistema nervioso simpático. Como en otros casos anteriormente descritos las glándulas mucosas del tracto respiratorio, en esta segunda observación, estaban distendidas y contenían una secreción espesa, pero había prácticamente una ausencia de células caliciformes. Consecuentemente el examen histológico de los pulmones era completamente diferente que en el asma, enfermedad en la cual se considera que el sistema nervioso parasimpático está sobrestimulado. El autor llega a la conclusión que estos dos casos apoyan fuertemente la teoría de Farber según la cual la alteración básica en la fibrosis quística del páncreas es un desequilibrio del sistema nervioso autónomo, piensa sin embargo que estos casos no concuerdan con la hipótesis de Farber de trastorno hiperfuncional del sistema nervioso parasimpático, sino lo que sugiere es una disfunción o hipofunción de este sistema.

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Proceedings of the Section for Pediatrics and School Hygiene of the Swedish Medical Society

Meeting, November 25, 1950.

Y. Larsson and C. Wedholm: Somatic and Mental Views Regarding the Summer Vacation Camps of Diabetic Children.

A theoretical discussion regarding the most suitable type of lodging, during the summer holidays, for diabetic children took place in connection with the establishment, during recent years, of special so-called Summer Vacation Colonies for such children. This discussion brought about an investigation during the summer of 1950, at the Hamra Barnkoloni (Children's Summer Home for Diabetic Children) with a view to studying the mental and somatic aspects of the problem. A suggestion was made for restricting the number of children and increasing the staff of nurses. It was also suggested that children who tolerate insulin less well should be separated and sent to convalescent homes or similar institutions. From a mental point of view, mention was made of the want of an adequate differentiation of the children, e. g., those unripe for "colony" life to be directed to summer homes. In addition, the importance of a really competent staff for organizing games, of selecting suitable games and the development of other means of occupation and pastimes during the summertime, was emphasized. Such negative mental effects as have been noticed have been entirely counterbalanced by positive factors. Vacation colonies for diabetic children are, it is maintained, not to be regarded only as an emergency measure but as an important link in the mental hygiene, among other measures serving the object of promoting the mental adaptation of diabetics.

Y. Larsson, K. G. Plomán and the late A. Lichtenstein: Late Complications in Juvenile Diabetes Mellitus with "Free" Dietary Treatment.

An account is given of 257 cases of diabetes in Stockholm-children given free dietary treatment. The mortality was 6.9 per cent, being lower than in comparable cases given fixed dietary treatment abroad. In 106 cases, the duration of the disease exceeded 10 years. The frequency

of retinopathy increased with the duration of the diabetes and, after 15 years, retinopathy was noted in 72.7 per cent. However, only 4.8 per cent of these cases had retinopathy in Stage III. (Stage I had microaneurysm and hemorrhage, II effusions, III connective tissue proliferations in the retina.) The frequency of retinopathy was no greater than in groups treated with a fixed diet. Albuminuria occurred in 15.6 per cent and peripheral arteriosclerosis in 7.9 per cent. The frequency of arteriosclerosis fell considerably below that found by WHITE whose cases were treated with a fixed diet. Hypercholesteremia occurred in 25 per cent, and a rise in blood pressure in 26 per cent. The albuminuria was closely correlated with the retinopathy. 93 per cent of the albuminuric cases had also retinopathy. The causes of the late complications are unknown. The complications appear to be of the same frequency whether the patients be on a fixed regimen or not. Since a free diet offers the diabetic children opportunities of leading practically normal life, it is superior to the other fixed dietetic methods.

G. Carlström, L. Ström and B. Vahlquist: The Renal Function in Diabetic Children given "Free" Dietary Treatment.

Apart from routine examinations for albumin, sediment, NPN and blood pressure, the renal function of 18 children, aged 6—15 years, was examined with inulin, paramino hippuric acid, and radioactive phosphorus. The duration of their diabetes varied from 3 to 10 years. Apart from insulin (for the most part a combination of protamine and regular insulin) they have all been on a free diet from the beginning. Of the functional tests, that of the phosphorus isotopes (using the method devised by STRÖM) disclosed a definitely reduced renal function in three cases where the disease had been present for 8, 9 and 10 years. Further, this test has revealed an isotope retention in 3 cases without any clinical signs of renal disease. Two of these 3 cases were girls of 12 and 14 years of age who had had their diabetes for 7 and 13 years, respectively. The elder girl had also a pronounced retinopathy. Both have shown a relatively marked insulin intolerance and have on several occasions been admitted to hospital in a precomatose state. In addition, the elder girl had symptoms of liver damage. A liver puncture disclosed signs of a fairly marked accumulation of fat and glycogen. Two of these cases had also hypercholesteremia. The third case is less definite and has not been so closely examined. In one of the cases with renal disease, the creatinine clearance showed reduced filtration. We have not felt justified in drawing any definite conclusions from the inulin clearance. The values of the PAH-clearance lie, without exception, within normal limits. It is noteworthy that the clearance tests, applied in the present cases, do not correspond to any reduced function, not even when an evident phosphatic retention has been ascertained. 1) In clinically uncomplicated cases of

diabetes, the renal function appears to be normal, though a reduced isotope clearance may constitute an initial symptom of diabetic renal damage. 2) In cases of diabetic renal disease with clinical symptoms, a phosphatic retention seems to occur, as a sign of renal damage.

B. Söderling: Mental Hygiene and Religious Dogmatic Superstition.

In the dogmatic world that is presented in "Grunden" ("The Foundation"), a text-book written by Bishop Bo GIERTZ for use in the confirmation courses, children absorb a feeling of contempt for intellectual values. They are made to accept self-confident statements regarding supernatural, entirely unprovable matters. The book is, in addition, stamped by an arrogant intolerance and lack of human understanding. It is apt to create feelings of guilt about natural impulses essential to human life. Moreover, it will produce, or nourish, a fear of death, and of the horrors of hell with its eternal punishment, the ultimate aim being to serve a common profane desire for power disguised in a religious mantle. A notable number of theologians have backed up Dr. Giertz and "Grunden" which, in their opinion, is based on the declared doctrines of the State Church, though possibly lacking too much in nuances. If this view is to be accepted as correct, i. e., if Dr. Giertz' teaching proves to be true to the confessions of the Church, the State authorities will have to choose between these dogmas and the human souls, i. e., between, on one hand, the teaching of the official theologians and, on the other, the principles underlying its own work for a preventive mental hygiene. Either the State will have to abandon its responsibilities or insist on other qualifications in its religious teachers and on changes in the doctrinal system. Since we object, nowadays, to fear and terror as educational principles and, on the contrary, are trying to proceed on positive lines, the State authorities need hardly be too remorseful, should they decide on such an action, considering particularly that dogmas are human inventions and, therefore, neither holy nor indispensable, but rather part of a past cultural stage. Furthermore, a religious faith ought to be allowed to be what, in fact, it is, a private matter, and no business of the State. Finally, all reason seems to show that the Christian orthodoxy is the great enemy of Christianity, if the Christian faith is to be identified with the message preached in life and words by its spiritual Master.

Ake Gyllenswärd: Asthmatic Attacks of an Unusual Etiology.

For two months, a boy, 10 months old, had several asthmatic attacks. On the present occasion, it was very severe. In spite of a comprehensive anamnesis and search for an allergen at home, no eliciting cause was

found. After another severe attack some months later, exposure tests with various allergens were tried. The asthma was found to occur only in the presence of the mother. At a further test with the mother some days later, the attack could not be reproduced. The only difference was that the previous occasion was connected with menstruation. The patient was now exposed to menstruating women and, when they were at the beginning of the menses, asthma attacks were produced. On a later occasion, when the mother had no menstruation, the family visited the country and an asthmatic attack occurred. She travelled with the boy on her lap to hospital, a journey of several hours, the attack gradually increasing in severity. At the hospital, she remained at his bed-side, the boy the whole time being in an extremely severe asthmatic state, which proved practically unaffected by any attempts at treatment. In the morning, the mother left the room, and the asthmatic attacks gradually abated, without the application of any further therapy. A few hours later, she reported that her menstruation had begun. Hyposensitization with a Coca extract of menstruum was performed and, in the following course, the symptoms were inconsiderable. An euglobulin, called menotoxin, has been ascertained in women 24 hours before the actual beginning of the menstruation, and during its first days. This is believed to be the allergen in the present case.

Bo Vahlqvist: The Antibody Defence of Prematures.

Premature infants are extremely susceptible to infections. This group of diseases rank second among causes of death. Various factors contribute to the weakness of their defence against infection. But few of these factors have been sufficiently analysed. Antibodies are being transferred from the mother to the child in the uterus. Recent investigations of antistreptolysin and antistaphylolysin (VAHLQUIST *et al.*, *Lancet* 1950; II: 851) show that these types of antibodies appear in the fetal blood only after the middle of pregnancy. Prematures possess antibodies in concentrations comparable to those of infants born at term. This seems to apply also to diphtheria antitoxin (DANCIS, personal communication). Only in the lowest weight groups do the titres fall notably below those of full-term children. The capacity of premature children to produce antibodies has been insufficiently investigated. In collaboration with F. NORDBRING, the present author has studied the effect of vaccination of newborn premature children with diphtheria toxoids. Not only was the response to one single injection delayed, as in the case of full-term newborns, but the final titres also fell much below those of the latter. Several prematures failed to show any response whatever. This slow, and insufficient, response to antigens will, probably suffice to explain the predisposition of prematures to septicemias.

DISCUSSION. — *C. Malmnäs:*

During pregnancy, the fetal surroundings are sterile, and, according to present opinion, the fetus is likely to imbibe and aspirate liquor amnii. This can be shown, *inter alia*, by injecting a roentgen contrast medium in the amnion. When the membranes break, there is a possibility of infection from the liquor amnii and, consequently, the fetus is exposed to the risk of being infected, should it aspirate or imbibe the waters. In cases of premature birth, this risk may, perhaps, be particularly marked. Normally, a fairly rich bacterial flora is to be noted in the upper part of the vagina and the cervical canal, *inter alia* staphylococci, occasionally coli, but more rarely streptococci. In fetuses that die, in the course of parturition, bacteria are ascertainable in the lungs, and the intestinal canal. Since infected liquor is often found, it is rather a matter of surprise that such infections of the fetuses are not more frequent. In all likelihood, the antibody defence offered to the fetus, by means of the placenta, plays a considerable part in this instance. In this connection, an interesting contrast is provided between the antistreptolysin (AST) and antistaphylolysin (ASta) titres, on one hand, and the coli agglutinins, on the other. Like Professor Vahlquist, I have found that the antistreptolysin and antistaphylolysin titres are low during the first half of the fetal life, increasing considerably during the later fetal months. From an electrophoretic examination, I have found that the increase in the content of gamma globulin is approximately parallel to the rise in titres. In investigations of coli agglutinins in blood from mothers and umbilical cords, performed in collaboration with C. A. ADAMSON and S. LÖFGREN, I have observed that coli agglutinins do not, as a rule, pass through the placenta. In a comparative examination of the antistreptolysin and antistaphylolysin titres in the colostrum and maternal blood the AST was found to be somewhat higher in blood than in the colostrum. As far as the ASta was concerned, the difference was much more marked. When comparing the agglutination titre in maternal blood and the colostrum during the first 48 hours after parturition, the agglutination titre of maternal blood somewhat exceeded that of the colostrum with O antigen, while with H antigen the reverse occurred. In veterinary medicine, it is a known fact that it is very important to administer colostrum to newborn calves. Even though no direct comparisons can be drawn when human beings are concerned, the relatively high content of antibodies in the colostrum, particularly with regard to coli agglutinins, apparently justifies an administration of colostrum to all newborns, and especially prematures, as soon as possible after parturition.

J. Lind and C. Wegelius: Heart Dynamics in Total Block.

Cases of total heart block are infrequent though not exactly rare. More than 200 cases have been described in the literature. These cases have attracted much attention, and the patho-anatomic basis, as well as the clinical symptom complex have been carefully studied. Electrocardiography and the recording of the arterial and venous pulse curves, have meant a great deal in the study of the patho-physiologic process. Two cases of block in adults where catheterization has been performed have been published recently (COURNAND and collaborators 1949). So far, no angiocardiograms have been reported in these instances. Such angiocardiograms should provide opportunities for supplementary observations of use for an estimation of the heart dynamics. At Norrtull's Hospital, Stockholm, a patient with a total heart block was admitted this autumn. Angiocardiography was performed according to the method elaborated at that hospital, with a view to studying the heart dynamics (synchronous photography in perpendicular planes, picture speed of 10 per second).

The patient was a girl, aged 3 1/2 years, with a retarded physical and mental development (length 89.5 cm, weight 9.5 kg, began to walk at an age of 18 months). The mother had noticed that physical exertion put her more out of breath than other children of the same age. During the three months before admission, the child had suffered from repeated attacks of unconsciousness.

The following notes were made at the physical examination: no cyanosis or dyspnea. *Heart*: harsh systolic murmur with point of maximum intensity in I: III sin. Slow, regular rhythm. *ECG*: total block. *Heart X-ray*: moderate general enlargement. *Angiocardiography* performed on probable diagnosis of interventricular septum defect with total block. This diagnosis was confirmed. Among the observations from the series of pictures of the heart dynamic the following points should be quoted: the heart works slowly and with a big stroke volume which causes a moderate permanent dilatation of the pulmonary artery. The passage of the relatively big stroke volume also produces a considerable dilatation of the pulmonary artery and the aorta in ventricular systole. When an auricular systole occurs while a ventricular systole is in progress, no contrast medium can pass through the atrioventricular valves. Instead, a strong venous reflux occurs down into the left inferior cava. As soon as the ventricular contraction ceases (where the T-wave passes over into the iso-electric line), the auricles will, however, empty into the ventricles, even though the auricular contraction may already have come to an end. As long as the ventricular diastole is at its maximum, the auricles will, broadly speaking, retain their systolic shape and size, irrespective of their own cardiac phase. Reversely, they will also keep their diastolic shape and size, as long as the ventricles remain systolically

contracted, owing, probably, to the available space in the pericardial sac. If the movements of the atrioventricular septum should be compared, roughly, to those of a piston, it is evident that, for mechanical reasons, the auricles, in ventricular diastole, when the piston occupies its highest position, cannot be completely filled. The ventricular part encroaches too much on the space. The auricular filling can take place, in its entire extent, only when the piston moves downward, in ventricular systole. When the piston remains in its lowest position (ventricular systole), the auricles cannot entirely empty into the ventricles, nor can they do so by a venous reflux, since the upward movement of the piston is necessary for an effective evacuation.

B. E. Hesselman: Case of Congenital Tuberculous Infection.

The child was delivered by cesarean section in August 1949 and immediately isolated from the mother who died a few hours later with tuberculous meningitis, confirmed at post mortem. The placenta was not examined. Weight at birth 3.400 g. To begin with, the child developed well. The tuberculin reaction was, immediately after delivery, uncertain. At an age of 2 weeks, subfebrile temperature, slight dyspepsia and loss of weight. Mantoux test 1 mg. now positive. Lumbar puncture revealed monocytic meningitis with acid-fast rods in direct preparations. Culture of the spinal fluid for tubercle bacilli nevertheless negative. At the same time, tuberculid-like epidermal changes. Patho-anatomic diagnosis disclosed foci of a probably specific inflammatory (tuberculous) nature. When the child was 3 weeks old, streptomycin treatment was stated, intrathecally for 2 months and subcutaneously, intermittently, for six months. Repeated X-ray examination showed, without exception, clear lung fields. However, at an age of 5 weeks, a spindle-shaped soft tissue elevation appeared in front of the lower part of the thoracic spinal column at a level between T 8—T12. This elevation gradually increased in size to a considerable extent, while a number of amorphous calcifications began to appear within it. No roentgenologic changes in the spinal column could be ascertained. After close on 9 months' treatment in hospital, the child was discharged, without any sign of an active tuberculous infection. The general condition was good. The development of the child was also satisfactory for its age, with no indication of cerebral or vestibular damage. The course has continued to be normal and, at an age of 16 months, the child appears completely healthy. In this case, a transplacental congenital tuberculous infection is surmised. As a result of streptomycin treatment, the course has, so far, been favourable, and the prognosis is regarded as good.

DISCUSSION. — *A. Wallgren* mentioned that two more Swedish cases of congenital tuberculosis had been published (*Miller-Wallgren. Pulmonary Tuberculosis in Adults and Children. Nelson. New York. 1939. — Revista Esp. de Ped. 4: 264. 1948*). He also called attention to some cases of congenital tuberculosis successfully treated with streptomycin reported by *Lesné et al. (Sem. des. Hôp. 25: 2083. 1949)* and *Amick et al. (Pediatrics. 6: 384. 1950)*.

M. Stahlman, P. Karlberg and J. Lind: Studies of Total Hemoglobin Content and Blood Volume during the First Period of Life.

In the past year, at Norrtull's Hospital, we have studied the total hemoglobin content and blood volume during the first 4—6 weeks of life. In so doing, we have applied the CO-method, elaborated by *Sjöstrand* for adults but modified, in this instance, for infants. The principle of the method is as follows: the child is made to respire in a close system filled with oxygen to which is added a small, exactly measured, amount of CO. The blood absorbs the CO until a balance has been reached between the content of CO in the blood and the gas mixture. The CO content of the gas mixture is analysed by means of a CO-meter. From this the blood concentration can be calculated mathematically. The small amounts of CO that the blood normally contains must first be determined. When the increase in concentration and the absorbed amount of CO are obtained, the total amount of Hb can be calculated. The material comprises 21 children with a birth weight of 2—4.8 kg. During the first week, practically daily determinations were made. During the second week, determinations were performed twice, during the 3rd—4th weeks once or twice and, finally, when possible, one determination was made in the 5th—6th weeks. The material has been divided into two groups, the first comprising cases where only determinations of the total hemoglobin content and Hb concentration in finger blood have been made. From these values, the blood volume

has been calculated according to the formula: $Bv \text{ in ml.} = \frac{\text{total Hb} \times 100}{\text{Hb in g. \%}}$.

When the values thus obtained and the body weight are compared to the age of a child, the Hb concentration will be found to fall, in the known manner, from about 18 g. per cent at birth to 15—13 g. per cent within, approximately, 4 weeks. The total amount of hemoglobin keeps, however, on a constant level, while the increase in the blood volume is parallel to the body weight. During the first month of life, a dilution of the blood will be found that may explain the physiologic anemia of the newborn.

In the second group, including 12 children the total of hemoglobin, as well as the plasma volume, were determined with Evans' blue, com-

prising a venous test of 8—12 ml. of blood in each determination. In cases where such determinations have been made four times during the first month of life, involving a loss of about 8 g. of Hb or approximately a fourth of the total amount, a reduction will be noticed also in the total hemoglobin content. Even after 3 determinations of the plasma volume, a tendency to a reduction seems to appear, especially when an additional unfavourable factor is found, e.g., anemia in the mother during the last months of pregnancy, infection in the child, etc.

When the physiologic changes in the blood of an infant immediately after birth are to be studied, methods implying repeated large blood samples are unadvisable, seeing that they may affect the condition of the blood in a child.

The values of the blood volume, calculated by means of a hematocrit from the plasma volume, lie considerably above those obtained by the CO-method. One of the reasons for this is, probably, that the hematocrit value (the Hb concentration) is not representative of the entire blood mass.

M. d'Avignon and K. A. Melin: Congenital Hypothyreoses Examined by Electro-encephalography.

42 cases of congenital hypothyreosis have been followed up by electro-encephalography. The original diagnosis was determined by pediatricians. The patients were examined at ages varying from 3 to 28 years. The purpose of the investigation has been to compare the electro-encephalographic findings to the mental development of the patients as judged by the Terman-Merrill tests. The particularly pronounced electro-encephalographic changes include, in the first place, the occurrence of pathologically slow waves, with a certain widening of the amplitude, occasionally collected in frequencies of varying lengths. In all instances, the recorded changes have been general. No hemispheric asymmetries or focal findings have occurred. 9 of the distinctly pathologic curves were found in the lowest groups of retarded mental development. In the groups of intelligence quotas of 70—90 and 90—110, only one markedly pathologic electro-encephalogram was noted. The less pronounced electro-encephalographic changes, with a moderate dysrhythmia, or a moderate slowing down of the curve, are chiefly represented in the intermediate groups. The normal electro-encephalographic curves are only to be seen in patients with normal, or practically normal, intelligence quotas. From this, one can probably conclude, that, in patients with a retarded mental development of this type, cerebral damage has occurred, in so far as a pathologic electro-encephalogram can be supposed to result from such a damage.

C. G. Bergstrand, B. Hellström and B. Jonsson: The Effect of ACTH on the Eosinophile Leukocytes in Premature and Full-Term Children.

The reduction in the number of eosinophile leukocytes 4 hours after a single dose of ACTH has been studied in children classified in 3 groups, as follows: 1) Newborn, full-term infants. 2) Full-term infants at an age of 1—3 months. 3) Premature infants. Altogether, the investigation comprised more than 100 determinations. In addition, for the purpose of control, the spontaneous 24-hour-reactions have been examined. The investigation showed that, in the great majority of cases, the number of eosinophile leukocytes in the blood remained constant during 4 hours but that, occasionally, a decrease or increase not exceeding 50 per cent of the original value, would occur. Full-term newborns revealed a distinct reduction in the number of eosinophils 4 hours after an ACTH-injection, though considerably less pronounced than that observed in adults, or the decrease noted in children at an age of 1—3 months. This effect was obtained with a dose of ACTH correlated to the body weight, corresponding to 25 mg. in adults. A dose of twice or four times that amount did not increase the effect. Premature infants reacted less than full-term ones, but the effect varied greatly from one case to another, without any definite correlation to body weight or age. Cortisone had no effect on the eosinophils in full-term newborn children.

P. Hedlund and H.-O. Mossberg: Chloromycetin in Pertussis.

Children in different stages of pertussis admitted at the Epidemic Hospital, in Stockholm, have been treated with chloromycetin per os. Every other child have been given chloromycetin (7 children <1 year of age, 17 children >1 year) and the rest (6 and 16, respectively) an inactive powder. The result are as yet preliminary. They show that *Haemophilus pertussis* will be killed by chloromycetin, and no longer ascertainable; that the course of the disease, when treatment is given during the catarrhal stage, will probably change; that a certain effect can be noted in infants in the paroxysmal stage; but that this effect is totally absent in children in the paroxysmal phase above that age. Alongside these continuing investigations, we are attempting to shed light on the effect of a chloromycetin treatment on the immunity of children. Until definite results have been obtained, caution should be observed in the application of chloromycetin in cases of pertussis. It should be used only in sick infants and, possibly in weak and tuberculous older children in the catarrhal stage of the pertussis.

Anders Hagströmer: A New Malformation Factor?

In an earlier study of 184 cases of harelip and/or cleft palate, the significance of the mother's age was investigated. A greater frequency was found among children of mothers of 21—25 years of age, as well as of those above 34 years ($P < 0.01$). In a second study a selection was made of 26 sibships (169 brothers and sisters) with more than one affected sib, and no known malformation inheritance. After the first defective child, the mother was found to be significantly more likely than before to give birth to a malformed offspring ($P < 0.001$). In a third study, the present author performed a field investigation of 100 cases of malformation. A significant correlation was found between a coitus interruptus and a malformation ($P < 0.001$). The positive results of these three investigations on the etiology of harelip and cleft palate suggest the existence of one, or several, unknown exogenetic malformation factors. At least one such factor now appears to have been definitely traced. That harelip and/or cleft palate in some cases originate in a coitus interruptus is, at any rate, a possibility that cannot be ruled out. The investigation suggests that coitus interruptus may in some cases cause various types of malformation.

Maj Levander-Lindgren: Follow-up Study of Scarlet Fever Patients with Electrocardiographic Changes.

The material comprises altogether 3 000 patients at the Epidemic Hospital in Stockholm, 2 700 being children. In 225 cases, the follow-up examinations took place 1—3 years after the disease, with a view to analysing electrocardiographic changes of a doubtful nature, as well as to elucidating, in cases of myocarditis, the symptoms and prognosis. *Questionable electrocardiographic changes:* A great many deviations from the normal that have been constant from one year to another, such as prolonged conduction times and intraventricular conduction defects, even bundle branch block, have, apparently, occurred independently of the scarlet fever. They are probably often of a constitutional and hereditary nature and will sometimes be found in several children of the same parents. Electrocardiographic changes, suggestive of an origination in vegetative changes or variations in the position of the heart, are deducted from the myocarditis cases, provided they can be reproduced at experimental tonus variations, and at such variations as occur in dorsal, lateral and abdominal positions, respectively. *Myocarditis* was diagnosed in 39 adults and 111 children. In spite of the fact that the electrocardiographic changes have, as a rule, been mild, they have produced cardiac symptoms in one third of the patients. Half of this number have complained of being increasingly short of breath. In several cases, precordial pains, and also a typical angina pectoris, have occurred,

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FROM THE DEPARTMENT OF CHILD HEALTH, GLASGOW UNIVERSITY, AND
THE WARDS AND PATHOLOGY DEPARTMENT OF THE ROYAL HOSPITAL
FOR SICK CHILDREN, GLASGOW.

Chronic Acidosis in Infants due to Renal Tubular Deficiency: Its Association with Metastatic Calcification

by

JAMES H. HUTCHISON and A. M. MACDONALD

In recent years there have been several reports in the British and American literature of a syndrome occasionally met with in infants, the outstanding features of which are hyperchloraemia and metabolic acidosis. Nephrocalcinosis has also been encountered in some of the cases. The pathogenesis of the condition appears to be a renal tubular insufficiency, although the underlying cause (or causes) of this remains unknown.

It is the purpose of this communication to review the literature, and to present the results of a study of four more infants who suffered from chronic acidosis apparently due to renal tubular insufficiency. One of these infants (Case 4) presented some additional features which, as far as the authors have been able to ascertain, have not previously been described in this disorder.

Historical Review

In 1933, at the International Paediatric Congress, LIGHTWOOD (1934) described four cases of infants who had failed to thrive and had died with renal failure. At autopsy he had found tubular infarcts of calcium salts. To this syndrome he applied the name *calcinosis infantum*. Two years later, at a meeting of the British Paediatric Association, he (LIGHTWOOD, 1935) stated that out of 850 autopsies performed in the Hospital for Sick Children, Great Ormond Street, six infants without underlying renal disease showed heavy deposits of calcium salts in the renal tubules. The

clinical records showed certain common features; — anorexia, constipation, failure to thrive and frequent vomiting. In one instance, calcium was found to be deposited in a medium-sized artery in relation to the internal elastic lamina.

In 1936, in America, BUTLER, WILSON and FARBER (1936) reported the cases of four infants who clinically and at autopsy shared some constant features, viz.; — failure to thrive; dehydration in the absence of excessive diarrhoea or vomiting and in the presence of adequate food, salt and fluid intake; hyperpnoea; elevation of serum chloride and acidosis; deposits of calcium salts within and adjacent to some renal tubules. In one case the urine was alkaline, in three acid. These cases clearly were identical to those described by LIGHTWOOD (1934; 1935), and in addition the striking features of acidosis and hyperchloraemia had been added to the syndrome. In a footnote to their paper, BUTLER *et al.* (1936) describe the case of a ten-year old boy with late rickets, low serum phosphorus and X-ray evidence of diffuse calcium deposits in the kidneys. This boy had the same type of hyperchloraemia and chronic acidosis as the infants, and the question arises as to whether he showed the possible late effects of the same syndrome.

LIGHTWOOD, MACLAGAN and WILLIAMS (1936) described a case of a fourteen months infant who had suffered from anorexia, vomiting, constipation and loss of weight for seven months. There was persistent acidosis and some hyperchloraemia. The X-rays failed to reveal evidence of nephrocalcinosis. The urine was usually alkaline and grew streptococci on culture. In hospital the patient developed diarrhoea but ultimately appeared to make a spontaneous recovery.

HARTMANN (1939) described the case of a four months old infant who from the age of two months had suffered from listlessness, anorexia, vomiting and bouts of dyspnoea. Severe acidosis which was demonstrated on admission to hospital was relieved by parenteral sodium-r-lactate but it recurred. It was then discovered that the urine had constantly a pH approximately that of blood, despite the fact that the loss of BHCO_3 into the urine would lead to severe acidosis. It was noted, also, that blood samples were characteristically in the zone of acid excess or

BHCO_3 deficit acidosis, and that treatment with sodium-r-lactate restored them to a position more nearly normal. HARTMANN (1939) considered that the condition was due to the persistent excretion of BHCO_3 into the urine, this being the only evident expression of renal insufficiency. The infant finally made a complete recovery after treatment with sodium-r-lactate.

ANDERSON (1939) reported a study of 31 cases of renal calcification in infants and children. Five cases resembled those described by BUTLER, WILSON and FARBER (1936) although details of the blood chemistry are not given. It is obvious, however, that renal calcification may occur in a wide variety of otherwise dissimilar conditions, and it would appear not to be a constant feature of the syndrome under review.

PETERMAN (1945) described the case of a two months old infant who was admitted to hospital with pyuria due apparently to infection with *E. coli*. This did not respond to treatment with several different sulphonamides. The other peculiar features were a chronic acidosis, persistently alkaline urine and air-hunger. Alkali therapy on frequent occasions brought about temporary improvement. At autopsy the kidneys did not show the usual appearances of bacterial pyelonephritis. The main histological findings were signs of epithelium damage in the collecting, and to a lesser degree, in the convoluted tubules, and also the presence of calcium deposits within many tubules. This case seems to have been another instance of the syndrome under review although it presented some unusual features.

In 1946, LIGHTWOOD reported another case of calcinosis infantum in an infant aged seven months with a history of vomiting, anorexia, loss of weight and constipation of one month's duration. She was wasted, dehydrated and fretful. The urine was neutral, contained a trace of albumin and numerous pus cells; culture was sterile. No detailed blood chemical findings were reported. At autopsy the kidneys showed many foetal glomeruli with marked cloudy swelling of the convoluted tubules. Occasional glomeruli and convoluted tubules showed deposition of calcium sand. Some collecting tubules showed deposition of calcium in the lumina. Some deposits of calcium also lay outside

the tubules. There was no foreign-body reaction around these deposits and no fibrosis.

At a meeting of the British Paediatric Association in 1948, two papers were read concerning idiopathic infantile acidosis and nephrocalcinosis. In the first one, MACGREGOR (1948) had studied 44 examples of renal medullary calcification and he concluded that although 24 belonged clinically to the group described previously by LIGHTWOOD (1934; 1935; 1936; 1946), precisely similar calcification was to be encountered in many other unrelated conditions. ANDERSON (1939) had previously reached similar conclusions. In the second paper, PAYNE (1948) then gave an account of seven cases which had been studied clinically in some detail. All seven patients were under the age of one year and had an illness consisting of anorexia, constipation, loss of weight, vomiting, hypotonia and dehydration. The urine contained leucocytes, epithelial cells, often a trace of albumin, was constantly sterile and often alkaline. A symptom present in half the patients was thirst. The blood showed persistent acidosis and hyperchloraemia but there was no departure from normal of the calcium or phosphorus levels. Treatment with a sodium citrate-citric acid mixture produced marked improvement. PAYNE went on to compare these cases with that of an older child with nephrocalcinosis, profound decalcification of the bones, muscular weakness and thirst, with albumin, blood and pus in the urine. In this child also there was hyperchloraemia and acidosis, but in addition there were abnormal levels of calcium and phosphorus (not specified). He decided that there was no conclusive evidence that this type of nephrocalcinosis was related to calcinosis infantum as described by LIGHTWOOD.

In 1949, BOUTOURLINE-YOUNG described the case of a five-and-a-half months old infant with a three weeks history of listlessness, loss of appetite, constipation, wasting and hypotonia. The outstanding findings were hyperchloraemia, hypertension, mild hyperphosphataemia and a tendency to develop dehydration easily. The plasma carbon-dioxide combining power was 41 vols. per cent which is a less severe degree of acidosis than that reported elsewhere in similar cases. At autopsy the kidneys showed heavy

calcium deposition in the collecting tubules although X-rays had not revealed this during life. The glomeruli appeared normal. There were no changes in the arterioles and capillaries to account for the hypertension.

During the same year, POWELL (1949) presented a case of nephrocalcinosis demonstrated radiologically at the Royal Society of Medicine. The clinical features in this fifteen months infant were anorexia, wasting, fretfulness, mild dehydration, hypotonia and severe constipation. The urine was alkaline, contained pus cells and grew *Proteus Vulgaris* on culture. The plasma bicarbonate was lowered, the serum chlorides and blood urea were raised. Calcium and phosphorus levels were normal. Marked improvement followed treatment with a sodium citrate mixture (6—12 g *per diem*).

STAPLETON (1949) has published a detailed description of a case of "idiopathic renal acidosis". An infant aged ten months was admitted to hospital because of chronic vomiting with obstinate constipation during the previous five months. In hospital she became dehydrated with deep respirations. The plasma bicarbonate level was markedly lowered and the plasma chloride level was raised. The urine was constantly alkaline to litmus. When the infant was given a sodium citrate-citric acid mixture (6 g sodium citrate daily) the plasma bicarbonate rose to the lower limit of normal. It was then found that the urine contained excessive quantities of bicarbonate (135—178 vols. per cent). At the age of thirteen months she developed a urinary infection which was successfully treated with sulphamezathine. At the age of fifteen months the citrate mixture was discontinued after nine weeks therapy. She remained well thereafter and appeared to have recovered. Tests for glomerular efficiency were within normal limits. There was no upset in the calcium or phosphorus blood levels and no X-ray abnormality in the skeleton. There was no X-ray evidence of nephrocalcinosis. STAPLETON (1949) considered that the mechanism of production of the acidosis was more probably an inability of the renal tubules to conserve bicarbonate than an inability to form sufficient ammonia. The striking feature in his patient, of course, was the continued

excretion of large amounts of bicarbonate in the urine in the presence of a severe acidosis.

KELSEY, REINHART and FISHEL (1950) studied two patients with "chronic acidosis of renal origin" aged eleven weeks and ten months respectively. Both had anorexia, vomiting, constipation, failure to gain weight and then the sudden onset of fever, signs of acidosis and circulatory collapse. The acidosis in the first patient was complicated by *B. Subtilis* septicaemia and pyelitis but persisted after the infection had cleared. In both patients essential blood changes were increased serum chloride and lowered plasma bicarbonate. In spite of the acidosis the urine was usually alkaline; in the second case the output of both urinary ammonia and titratable acid was low but the ratio was 1.4: 1. In the second case there was suggestive evidence of nephrogenic diabetes insipidus which was uninfluenced by pitressin tannate but was relieved by sodium bicarbonate. In the first patient X-ray studies are not reported but in the second there was no evidence of nephrocalcinosis and no bony abnormality. KELSEY *et al.* (1950) decided, by a process of exclusion, that the chief metabolic defect in their patients was failure of re-absorption of bicarbonate by the renal tubules. Detailed studies into the question of bicarbonate re-absorption were not found possible.

LATNER and BURNARD (1950) carried out some experiments in six patients with "idiopathic hyperchloraemic acidosis" to determine the reason for the persistent alkalinity of the urine in their patients. The finding of a high concentration of bicarbonate in the urine suggested to these workers that the incomplete re-absorption of this substance was due to a defect in the proximal tubule which is thought to be the site of absorption of all the bicarbonate present in the glomerular filtrate in the presence of acidosis (PITTS, AYER and SCHEISS, 1949). They gave their patients an intravenous infusion of an isotonic solution made up with disodium hydrogen phosphate and monosodium dihydrogen phosphate in the proportion of four to one and with a pH of 7.4. As a result of this infusion of sodium phosphate, the kidneys in their patients were found to be capable of secreting free acid to a degree comparable with controls, and of significantly increasing

the output of ammonia. Urinary bicarbonate excretion was excessive in the resting state, but from evidence provided by the partial pressure of carbon dioxide in the urine it was deduced that the distal tubule was re-absorbing bicarbonate in a normal manner, and that the proximal tubule was the site of faulty absorption. Furthermore, defective bicarbonate absorption in the proximal tubules may lead to an increased absorption of chloride (PITTS, AYER and SCHEISS, 1949) which may account for the hyperchloraemia of the disease. Continued failure of bicarbonate absorption would, also, lead to the presence of bicarbonate in fairly high concentration in the distal tubules. This would not only cause increased loss of bicarbonate in the urine, but would inhibit the excretion of free acid and ammonia by the distal tubule. In this way, the conservation of base would be completely upset, and its failure would result in a continued acidosis and consequent hypercalcuria, owing to the mobilization of calcium to neutralize acid radicals. LATNER and BURNARD point out, therefore, that the calcification and other pathological changes noted in the distal convoluted and collecting tubules in nephrocalcinosis infantum would be a result, not a cause, of the condition. They also suggest a biochemical diagnostic test for the disease. The test depends on the occurrence of a raised partial pressure of carbon-dioxide in the urine (above 50 mm of mercury) in the presence of a lowered alkali reserve. They also note that since in this disease a high proportion of the bicarbonate absorption occurs in the distal tubules, and as sulphonamide is known to inhibit carbonic anhydrase which is an important factor in *distal* tubular absorption this class of drugs would lead to an increase in the already severe acidosis, and should be avoided.

In the course of this review of cases of infantile renal acidosis mention has been made of two older children (BUTLER, WILSON and FARBER, 1936; PAYNE, 1948) who presented similar chemical changes in the blood — acidosis and hyperchloraemia — although the clinical picture was one of bone disease and quite dissimilar to that met with in the infant-cases. None the less, the identical blood changes and the presence of nephrocalcinosis in both types of patient suggests that some pathogenic relationship may exist.

It may, then, be not out of place to review briefly several other cases which have been reported in older children and adults.

In 1940, ALBRIGHT, CONSOLAZIO, COOMBS, SULKOVITCH and TALBOT reported the case of a thirteen year old girl with rickets and dwarfism, nephrocalcinosis, hyperchloraemia and acidosis. After extensive metabolic study they suggested that the syndrome was a renal tubular disorder with inability to secrete ammonia or to excrete an acid urine.

In 1942, BOYD and STEARNS described the case of an eleven year old girl with rickets, persistently alkaline urine, hypophosphataemia, lowered alkali reserve and diminished serum chloride. The daily excretion of ammonia was normal and in proportion to the total excretion of nitrogen. On treatment with sodium bicarbonate and vitamin D the rickets healed and the blood chemistry returned to normal. During her illness the girl had several unexplained attacks of weakness and paraesthesia; death occurred during a particularly severe attack. The authors postulated that the acidosis was the result of loss of fixed base from the body, even although the underlying cause for such loss was not clear. Histological examination of the kidneys showed only minimal pathological change. A few small areas of calcium deposition were found in the pyramids near the pelvis. BOYD and STEARNS (1942) suggested that the tubular dysfunction without evidence of damage to these structures might indicate that the fundamental disturbance was not in the kidney but some other tissue, possibly the diencephalon.

RULE and GROLLMAN (1944) reported a case of a girl aged fifteen years who suffered from rickets and spontaneous fractures from the age of fifteen months. The blood showed low plasma phosphorus, hyperchloraemia and low serum bicarbonate. There were multiple renal calculi.

In this country, BAINES, BARCLAY and COOKE (1945) reported the case of a woman aged twenty-nine years with polyuria, bilateral renal stones, raised serum chloride, low plasma bicarbonate and a urinary pH fixed between 6.7 and 7.1. X-rays of the bones showed no abnormality. She responded to treatment with a sodium citrate-citric acid mixture but died later of a severe

reaction to sulphathiazole. The histological changes in this patient were reported later by GOVAN (1950). The most marked feature was a gross degree of vacuolation of the epithelium lining the first convoluted tubules. This change may have had aetiological significance.

In 1946, ALBRIGHT, BURNETT, PARSON, REIFENSTEIN and ROOS, in the course of a long paper on osteomalacia, described eight cases in adolescents and adults of "renal acidosis from tubular-insufficiency-without-glomerular-insufficiency". All eight patients had osteomalacia; four had both nephrolithiasis and nephrocalcinosis, two had nephrolithiasis without nephrocalcinosis and two showed neither. Three patients had episodes of weakness similar to those described by BOYD and STEARNS (1942), and these were shown to be due to hypokalaemia. High serum chloride and low serum CO_2 content were characteristic. ALBRIGHT *et al.* (1946) suggested the following sequence of events; — (a) insufficiency of the tubules, cause unknown; (b) decreased ability to make ammonia and to excrete an acid urine; (c) demand for calcium as a base; (d) hypercalcaemia; (e) tendency to hypocalcaemia; (f) parathyroid hyperplasia; (g) hypophosphataemia; (h) failure to deposit calcium phosphate salts in the osteoid; and (i) osteomalacia. Treatment with alkalinizing salts stops further stone formation because of decreased calcium in the urine. The osteomalacia responds to vitamin D plus alkali.

Case Reports

Case 1. Ian McF. was an eight-months old male infant on admission to Hospital on 2nd August, 1950. The family history was irrelevant. He was breastfed for two months and thereafter received full cream national dried milk in adequate amounts. In July, 1950 he developed diarrhoea and vomiting. The stools were said to be loose and green but not more frequent than five per day. On 2nd August, he was a very dehydrated and gravely ill infant, 61 per cent of the expected weight for his age. Although he had neither vomiting or diarrhoea after admission and took oral fluids (half-strength physiological saline) well he remained so dehydrated that on 4th August intravenous drip therapy with plasma and 5 per cent glucose in quarter strength physiological saline was started with marked improvement. He was dismissed home on 19th August feeding

Table 1.

Case 1: Ian McF. Blood and Urine Chemistry.

Date	Blood N.P.N. mg%	Blood CO ₂ content vols. %	Plasma chloride mg%	Urine		Weight kg	* Treatment
				Bicar- bonate vols. %	Ratio NH ₃ / acid		
7.9. 50	—	22.0	—	—	—	5.66	Nil
8.9. 50	—	22.2	602.6	14.3	2.0	5.70	Nil
9.9. 50	—	—	—	—	—	5.72	Sod. Bicarb. 15 grains 5 x
13.9. 50	—	31.6	511.3	91.2	1.9	6.16	Do.
20.9. 50	—	32.3	541.1	89.4	2.2	6.26	Do.
24.9. 50	—	—	—	—	—	6.30	Sod. Bicarb. 30 grains 5 x
29.9. 50	—	26.7	582.1	106.0	1.4	6.31	Do.
3.10. 50	—	—	—	—	—	6.40	Sod. Bicarb. 45 grains 5 x
6.10. 50	—	57.8	510.1	203.7	1.2	6.58	Do.
16.10. 50	—	26.1	—	124.8	1.3	6.47	Do.
23.10. 50	—	31.8	502.5	94.7	—	7.09	Do.
6.11. 50	—	38.9	—	142.9	—	7.44	Do.
4.12. 50	—	33.6	—	127.5	1.7	8.24	Do.
3.1. 51	—	31.5	507.2	—	—	9.23	Do.

reasonably well but was still fretful and hypotonic. He was re-admitted to Hospital on 28th August because of continued irritability, anorexia, obstinate constipation and loss of weight.

Physical examination revealed an irritable and dehydrated infant who was now 69 per cent of the expected weight for his age. Hard faecal masses were palpable throughout the lower abdomen. Blood examination gave the following figures; — Hb. 10.64 g per cent; red cells, 3.63 million per c.mm.; white cells, 11,000 per c.mm. X-ray of the abdomen showed no renal calcification. X-rays of the long bones showed no abnormality. The urine contained no abnormal constituents.

Chemical Investigations of the blood and urine were started on 7th September because there was no obvious reason for the persisting dehydration (Table 1). The blood carbon-dioxide content was 22 vols. per cent; the plasma chlorides were 602.6 mg per cent. The serum calcium was 10.1 mg per cent; the blood phosphorus was 3.5 mg per cent. The urinary pH was 6.9. The urinary chlorides varied from 142 to 348 mg per cent. The ammonia-titratable acidity ratio was 2.02 : 1.

Treatment and Progress are shown in Table 1. As soon as sodium bicarbonate (15 grains five times daily) was started on 9th September, the infant showed enormous clinical improvement with return of appetite, gain in weight and loss of dehydration. None the less, the acidosis was not corrected even with 45 grains of sodium bicarbonate five times daily. Constipation required the regular use of laxatives. The enormous loss of bicarbonate in the urine (89.4 to 203.7 vols. per cent CO_2), even in the presence of a continued acidosis, should be noted. The plasma chloride levels fell after treatment with sodium bicarbonate was started. At no time was the ammonia-titratable acidity ratio below normal. The infant was dismissed home on 7th October and is thriving on 45 grains of sodium bicarbonate daily in spite of continuing acidosis.

Case 2. Stewart W. was a six-months old male infant on admission to Hospital on 15th August, 1950. The family history was irrelevant. He was breastfed for three months and thereafter was fed on full cream national dried milk. One month before admission to Hospital he quite suddenly and inexplicably became anorexic, fretful and severely constipated. Loss of weight and energy were marked. At times his breathing was "heavy", and his mother drew attention to a peculiar brownish tinge which had appeared in his skin.

Physical examination revealed a hypotonic, listless and dehydrated infant whose skin showed a muddy brownish pigmentation. He was 81 per cent of the expected weight for his age. Respiration was noticeably deep and pauseless. Palpation revealed many small hard faecal masses in the abdomen. Blood examination gave the following figures; — Hb. 11.34 g per cent; red cells, 3.86 million per c.mm.; white cells, 22,000 per c. mm. X-ray of the abdomen failed to reveal nephrocalcinosis. The long bones showed no radiological abnormality. The urine contained no abnormal constituents.

Chemical Investigations of the blood and urine were started on 16th August (Table 2). The blood carbon-dioxide content was 21.2 vols. per cent; the plasma chlorides were 645.8 mg per cent. The serum calcium was 9.9 mg per cent; the blood phosphorus was 3.6 mg per cent. The urinary pH varied from 6.8 to 7.2 before treatment. The urinary chlorides varied from 191 to 212 mg per cent. The ammonia-titratable acidity ratio was 2.23: 1.

Treatment and Progress are shown in Table 2. Before treatment was started on 23rd August, the infant's condition remained as on admission. In addition he had brisk fever of unknown origin on 21st and 22nd August. When sodium bicarbonate, 15 grains six times daily, was started on 23rd August there was immediate improvement with disappearance of dehydration, return of appetite and energy. He was given 150 cc of citrated blood into a scalp vein on 30th August because the haemo-

Table 2.

Case 2: Stewart W. Blood and Urine Chemistry.

Date	Blood N.P.N. mg%	Blood CO ₂ content vols. %	Plasma chloride mg%	Urine		Weight kg	Treatment
				Bicar- bonate vols. %	Ratio NH ₃ / acid		
16.8. 50	—	21.2	645.8	—	—	5.60	Nil
17.8. 50	36.6	25.1	647.6	—	—	5.66	Nil
21.8. 50	—	21.7	578.6	19	2.2	5.82	Nil
23.8. 50	—	—	—	—	—	5.70	Sod. Bicarb. 15 grains 6 a
26.8. 50	—	41.7	566.9	—	—	6.10	Do.
30.8. 50	—	23.0	589.7	71.8	1.7	6.08	Do. ¹
4.9. 50	—	19.6	493.2	—	1.9	5.88	Do.
7.9. 50	—	—	—	—	—	6.21	Sod. Bicarb. 30 grains 5 a
11.9. 50	—	30.4	561.0	117.8	—	6.44	Do.
19.9. 50	—	25.4	597.9	—	—	6.20	Do.
26.9. 50	—	28.6	542.3	100.4	—	6.61	Sod. Bicarb. 45 grains 5 a
3.10. 50	—	26.1	517.1	—	—	6.67	Do.
10.10. 50	—	45.2	—	—	—	6.78	Do.
31.10. 50	—	29.2	—	199.4	1.5	6.95	Do.
28.11. 50	—	35.8	—	² 32.9	2.3	7.22	Do.
26.12. 50	—	37.7	584.4	—	—	7.70	Do.
9.1. 51	—	43.3	475.6	154.3	—	7.80	Do.

¹ Blood Transfusion, 150 cc citrated blood.² Sod. Bicarb. vomited because of struggling during past week.

globin level had fallen to 9.52 g per cent. On 2nd September, he again had brisk fever with return of dehydration, severe constipation, air-hunger and hypotonia. The blood carbon-dioxide which had risen to 41.7 vols. per cent on 26th August was 19.6 vols. per cent on 4th September. The fever settled spontaneously on 4th September, but the infant's condition did not improve until the sodium bicarbonate was increased to 30 grains five times daily on 7th September. On 12th September, he was so well that he was dismissed home in spite of continued acidosis. He returned as an out-patient on 19th September when the abdomen was felt to contain many hard faecal masses. This was relieved by a rectal wash-out and he was given a laxative to take regularly. On his next out-patient visit on 26th September, the same state of affairs existed. On this date, the sodium bicarbonate was in-

creased to 45 grains five times daily. The acidosis was not corrected even on this dose of alkali but, thereafter, the infant thrived well, and his constipation was controlled by an occasional dose of laxative. The skin pigmentation completely disappeared. The same chemical changes were noted under treatment as in Case 1, viz; — the great loss of bicarbonate in the urine in the presence of acidosis (71.8 to 199.4 vols. per cent); the falling plasma chloride level; the persistently normal ammonia-titratable acidity ratio.

Case 3. Ann McC. was an eight-months old female infant on admission to hospital on 22nd June, 1950. The family history was irrelevant. She was breastfed for three months and was then given full cream national dried milk in adequate amounts. At the age of three-and-a-half months she began to vomit frequently after feeds. This remained unchanged on liquid cow's milk. At the age of five months she was referred to the hospital out-patient department where she was seen to be a lively but irritable infant who was 67 per cent of the expected weight for her age. Thickening the feeds with cereal produced temporary improvement in the vomiting. Her stools were hard but not unduly infrequent. Admission to Hospital was advised on 22nd June, 1950 because of continued vomiting and failure to thrive.

Physical examination in hospital revealed a hypotonic, slightly dehydrated fretful infant. The urine contained a trace of albumin; there were no pus cells and a culture remained sterile. The faeces contained trypsin. Blood examination gave the following figures; — Hb 14.7 g per cent; red cells 5.30 million per c.mm.; white cells 15,600 per c.mm. There was no radiological evidence of renal calcification or disease of the bones. A barium swallow showed no oesophageal abnormality.

Chemical Investigations of the blood and urine were first undertaken on 30th June (Table 3) in an effort to explain the infant's failure to thrive. The blood carbon-dioxide content was 26.3 vols. per cent; the whole blood chlorides were 644.7 mg per cent. The serum calcium was 10.0 mg per cent; blood phosphorus was 3.4 mg per cent. The urinary pH before treatment varied from 5.8 to 8.0. Urinary chlorides varied from 114 to 256 mg per cent. Urine examination by paper chromatography did not reveal amino-acids to be present in abnormal quantity or distribution.

Treatment and Progress are shown in Table 3. Treatment was started on 1st July with a mixture composed of 100 g sodium citrate and 60 g citric acid in 1 000 cc of water. The infant was given 6 g of the sodium citrate daily in six divided doses. This produced marked clinical improvement and the blood carbon-dioxide content rose to 61.0 vols. per cent on 3rd July. Unfortunately, on this date the infant developed fever and began to pass infrequent loose green stools; this did not respond

Table 3. Case 3: Ann McC. Blood and Urine Chemistry.

Date	Blood N.P.N. mg%	Blood CO ₂ content mg%	Plasma chloride mg%	Blood chlorides mg%	Urine		Weight kg	Treatment
					Bicarbonate vols. %	Ratio NH ₃ /acid		
30.6.50	72.4	26.3	—	—	—	—	4.91	Nil
1.7.50	—	—	—	—	—	—	5.02	Sod. Citrate 1 g 6 ×
3.7.50	42.0	61.0	—	644.7	—	—	5.12	Do.
5.7.50	25.5	68.9	—	—	—	—	5.19	Do.
7.7.50	27.2	53.3	—	465.7	—	—	5.22	Do.
12.7.50	25.5	53.2	—	483.8	—	—	5.22	Do.
14.7.50	—	—	—	—	—	—	5.30	Stop Treatment
18.7.50	27.8	30.0	—	471.0	—	—	4.98	Nil
21.7.50	56.8	31.0	—	519.5	—	—	4.88	Nil
23.7.50	—	—	—	—	—	—	5.00	Sod. Citrate 1 g 6 ×
26.7.50	—	40.0	—	—	—	—	5.10	Do.
29.7.50	62.6	36.0	—	561.6	—	—	4.98	Do.
4.8.50	42.4	65.3	—	571.0	—	—	4.94	Stop Treatment ¹
7.8.50	—	—	—	—	36.5	1.5	5.04	Sod. Citrate 2 g 6 ×
8.8.50	—	60.1	—	—	—	—	5.04	I-V M/6 Sod. Lactate 400 cc.
9.8.50	—	84.1	—	—	—	—	5.04	I-V Plasma 350 cc.
10.8.50	—	77.8	—	—	—	—	—	Do.
11.8.50	—	69.8	—	—	—	—	5.10	I-V 5 % Glucose 1/4 Saline 500 cc.
17.8.50	—	50.5	493.2	—	—	—	4.82	Nil
21.8.50	—	43.7	601.4	—	3.4	2.5	4.62	Nil
28.8.50	—	29.0	—	—	—	—	5.07	Nil
1.9.50	—	29.7	518.3	—	8.6	1.6	4.96	Nil
2.9.50	—	—	—	—	—	—	4.99	Sod. Bicarb. 15 grains 6 ×
5.9.50	47.6	45.6	490.8	—	—	—	5.02	Do.
7.9.50	—	49.3	553.4	—	108.0	2.0	5.05	Do.
6.10.50	—	36.9	484.8	—	78.6	1.5	6.79	Sod. Bicarb. 15 grains 5 ×
3.11.50	—	41.8	—	—	126.0	—	7.29	Do.
1.12.50	—	38.7	447.3	—	42.5	1.6	8.06	Do.

¹ Blood Transfusion, 300 cc. citrated blood.

to dietetic measures plus penicillin and on 7th July there was a sudden return of dehydration, hypotonia and fretfulness. The citrate mixture was stopped on 14th July because of continued fever and diarrhoea; on 18th July the blood carbon-dioxide had fallen to 30.0 vols. per cent. The urine remained free from pus and was sterile on culture. On 23rd July the citrate mixture was re-started; the blood carbon-dioxide rose to 40.0 vols. per cent on 26th July but fever, diarrhoea and dehydration persisted. Treatment with sulphamerazine produced neither improvement nor deterioration in the patient's condition. The citrate mixture was again stopped on 4th August, (when the blood carbon-dioxide was 65.3 vols. per cent) and a blood transfusion of 300 cc of citrated blood was given because the haemoglobin level had fallen to 8.4 g per cent. On 7th August, the sodium citrate was given in a total dosage of 12 g per day but fever, diarrhoea and dehydration persisted and were unaffected by aureomycin. On 8th August, 400 cc of M/6 sodium lactate were given by intravenous drip, followed during the next three days by plasma and 5 per cent glucose in quarter strength physiological saline. Although the blood carbon-dioxide during this period was above normal (60.1 to 84.1 vols. per cent) the intravenous therapy produced very little improvement. From 12th August until 2nd September, specific treatment was withheld and the blood carbon-dioxide fell to 29.7 vols. per cent on 1st September. Fortunately by 21st August the fever and diarrhoea spontaneously recovered although the infant remained dehydrated, fretful and hypotonic. On 2nd September, sodium bicarbonate 15 grains six times daily was prescribed. The blood carbon-dioxide rose to 45.6 vols. per cent on 5th September, and this was associated with marked clinical improvement. For the first time since admission the infant became eager to feed. Lest there should be a recurrence of ward infection the patient was discharged home on 9th September on sodium bicarbonate 15 grains five times daily. In spite of continued mild acidosis the infant has continued to thrive on this treatment. As in the two previous cases, the urine has contained large amounts of bicarbonate during the periods of alkali treatment.

Case 4. Susan W. was a fourteen-months old female infant on admission to hospital on 3rd June, 1950. The family history was irrelevant. She was breastfed for eight months, and thereafter was fed on Ostermilk No. 2 plus an adequate mixed diet containing soup, vegetables, eggs and cereals. From the age of eight months only she was given vitamin D, approximately 500 units *per diem*. She was thought to be healthy until two months before admission when it was noted that her teeth were decaying rapidly. She became anorexic, fretful with loss of weight and increasing pallor. For one month before admission, vomiting occurred daily. The stools were said to be normal.

Physical examination revealed a gravely ill infant. Dehydration, pallor and hypotonia were marked. The skin had a peculiar rubbery feel to palpation. She was 82 per cent of the expected weight for her age. The liver was palpable two finger-breadths below the costal margin and the spleen-tip was palpable. No other abnormal signs were detected on clinical examination. Blood examination revealed a severe anaemia; — Hb. 7.7 g per cent; red cells, 3.48 million per c.mm.; white cells, 17 600 per c.mm.; reticulocytes, 3 1/2 per cent; platelets 1 620 000 per c.mm. Films showed 15 per cent monocytes but no abnormal red or white cells. The bonemarrow showed hypoplasia affecting erythropoiesis and granulopoiesis alike. X-rays of the skull and long bones showed no abnormality. There was no X-ray evidence of calcification in the kidneys. Chest radiographs showed a diffuse, but not intense, mottling throughout both lung fields which was (erroneously) interpreted as indicating the presence of pulmonary congestion. The urinary pH varied from 6.0 to 8.0 before alkali treatment was started. The urine contained albumin but no other abnormal constituents and it was sterile on culture.

Treatment and Progress. On 3rd June blood transfusion by slow intravenous drip was started. On 4th June after 300 cc of blood the Hb. was 11.2 g per cent, but as dehydration was still marked the intravenous drip was continued with plasma and 5 per cent glucose in quarter strength physiological saline until 5th June. Penicillin and sulphamerazine were started on admission. In spite of this treatment the infant remained dehydrated although she was drinking well and vomiting was infrequent. The stools were normal. By 12th June the infant had become much more ill with brisk fever, frequent vomiting and intense dehydration. On this date dyspnoea was noted but there was no cyanosis. Blood chemistry was studied for the first time. The blood carbon-dioxide content was 23.5 vols. per cent; blood chlorides were 405 mg per cent; serum sodium was 241 mg per cent; non-protein nitrogen was 111 mg per cent. Unfortunately, calcium and phosphorus estimations were not made. On 13th June, blood examination revealed haemoconcentration; — Hb. 15.4 g per cent; red cells, 5.72 million per c.mm.; white cells, 30 400 per c.mm. On 14th June, treatment with sodium bicarbonate, 30 grains six times daily, was started. On 16th June, the blood carbon-dioxide content had been raised to 44.5 vols. per cent without any improvement in the infant's clinical condition. On 18th June, the infant was more ill with continued dehydration and fever; for the first time loose stools were passed on this date. The sodium bicarbonate was stopped and intravenous drip therapy with 5 per cent glucose in quarter strength physiological saline was re-started. On 19th June, the blood carbon-dioxide content was 88.0 vols. per cent. The infant died on 20th June.

Post-mortem Examination.

CHRONIC ACIDOSIS IN INFANTS

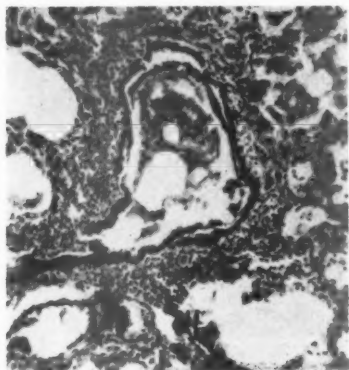


Fig. 1. Calcification of bronchiolar wall. The epithelium has become detached from the wall. H. & E.

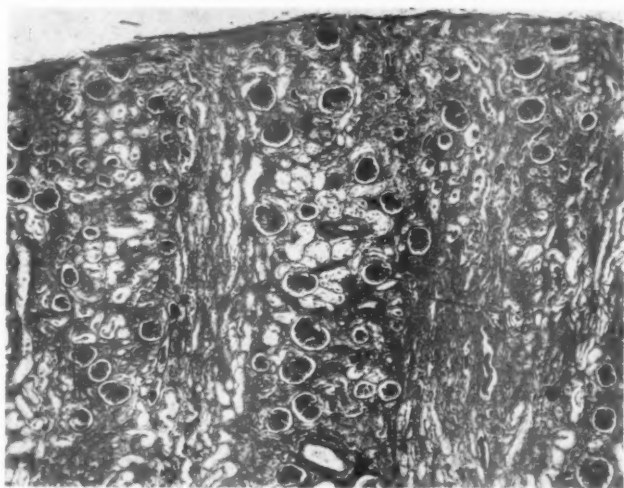


Fig. 2. General low power view of the kidney cortex. Gallego stain.

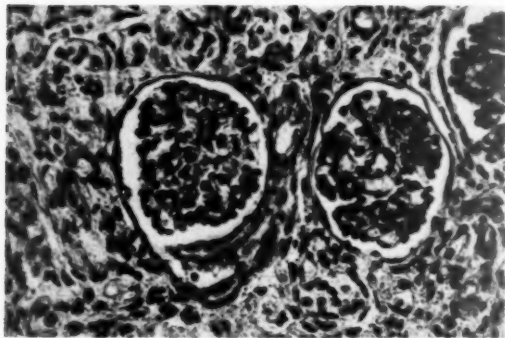


Fig. 3. The tubules are poorly developed round these two glomeruli. From one of them the origin of the proximal tubule is seen. The surface glomerular cells are more cuboidal and more primitive looking than normal. Gallego stain.

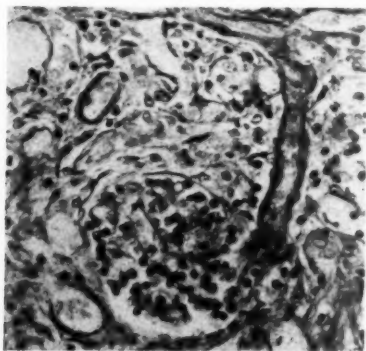


Fig. 4. Typical glomerulus with the thick basement membrane of the proximal convoluted tubule, two more cross sections of which are seen coming from the cortical surface. The cells of the tubules are flatter than normal. Gallego stain.

External Appearances. The body was that of a fourteen-months old female child weighing 7.06 kilogrammes.

Head. The total brain weight was 833 g. The meninges were normal. Multiple vertical sections of the brain were cut but no lesion was seen, and microscopically, routine sections from the motor area and the cerebellar cortex were normal. The pituitary gland was normal.

Neck. The larynx and trachea contained a mucopurulent secretion and the mucosa was congested. The oesophagus, thyroid and great vessels were normal. No para-thyroid enlargement was found in routine dissection of the structures of the neck and thorax. One thyroid lobe was examined histologically and was normal. The regional lymphnodes were very slightly enlarged due to oedema.

Thorax. The heart weighed 38 g and was within the normal range for the age of the child. The pericardium was normal. When the heart was opened a fleck of calcification was found on the posterior flap of the mitral valve. The other valves, the myocardium and the aorta were normal. Routine histological examinations of the coronary vessels and myocardium showed calcification in the walls of these vessels. The thymus was normal to the naked eye and histologically. The right lung was 85 g and the left 93 g. They were both within the normal range though the left lung was appreciably heavier than the right. The pleural surfaces were normal. Both lungs felt nodular, the left more than the right and at the autopsy this fact was considered to be due to the presence of bronchopneumonia, although the unusual firmness of the nodules was observed. The base of each lower lobe was congested and partially collapsed. The tracheo-bronchial lymphnodes were not grossly abnormal.

Histologically, three blocks of lung were examined and each presented a similar remarkable picture. There were widespread deposits of calcium irregularly scattered through the lung substance and affecting all the elements of structure. The calcium was most frequently lining the alveolar capillary or was in the capillary. It was found in the bronchiolar wall and at the junction between bronchiole and atrium. Some of the cartilage of the smaller bronchi was calcified. Giant cells were frequently seen in association with the alveolar calcification and the amalgamation of alveolar lining cells into giant cells was a common feature. Blood vessels, in particular veins, showed calcification of the muscle in their walls (Fig. 1). There was no fibrosis of the lung and though about half the alveoli contained an albuminous fluid with a few mononuclear cells in it, no pneumonia was present. The density of the calcification varied and was most marked in the alveolar walls though even here the intensity varied greatly from the earliest signs of calcification to a solid-looking black mass.

Considerable effort was made to establish what formed the calcified core. Van Kossa's stain for calcium was first used and was constantly positive. Then, in decalcified sections, Turnbull's Blue, Gomori, Berlin Blue and Prussian Blue were used to establish the presence of iron. By the standard methods the reactions were all positive repeatedly though the intensity of the reaction varied with the density of the calcium present. For the presence of elastic tissue orcein was used. All the deposits contained a core of fibres of elastic tissue, though occasionally the fibres were so fragmented that mere granules were seen. From a study of the sections it would appear that the earliest change is a condensation of the elastic fibres, then a local histiocytic reaction and then the deposit of iron and calcium. It seemed probable that a capillary thrombus had not been formed in the large number of examples, but it may have occurred on some occasions.

Genito-urinary System. The right kidney weighed 36 g and the left 30 g. Both showed well-marked foetal lobulation. The colour was normal and the capsules stripped easily leaving smooth surfaces sparingly studded with acute haemorrhages measuring 0.5 to 1.0 mm across. When cut, the right renal pelvis was slightly dilated but the left was normal. There were a few small stones like coarse sand-grains in the right pelvis. The medulla was congested in each kidney. The ureters and bladder were normal.

Under a hand lens the sections of the kidney gave the general impression of underdevelopment, difficult to define (Fig. 2). With a higher power, the glomeruli were slightly smaller than usual and more primitive in appearance, when compared to tissue of the same age. In many, the superficial layer of cells of the glomerulus were still cuboidal in type though not so clearly so as in the newborn. The glomeruli were more closely packed together than normal and the medullary rays broader. The close packing was due to a lack of tubular substance — the secreting tubules. Many serial sections from both kidneys were examined stained by the Gallego method. There was a mild increase in connective tissue, even in distribution, and not of an irregular pattern as would be found as a result of some previous inflammatory process but more probably due to condensation from atrophy. The surface of the kidney was smooth and regular except where the peripheral haemorrhages bulged. A comparison of the two kidneys was made and the cortical appearances were indistinguishable and any evidence of hydronephrosis imperceptible. In two hundred sections less than ten partially sclerosed glomeruli were found. The capsular basement membrane was occasionally slightly thickened but never showed unequivocal sclerosis. A striking feature was the clearly thickened basement membrane of the proximal convoluted tubule which could be traced with ease in the condensed parts of the parenchyma (Figs. 3 and 4). This was not a constant feature but could

be seen in every section. Some proximal tubular basement membranes did not show this appearance. Equally pronounced was the thinness of the proximal tubule. Hyaline casts were frequently found in the collecting tubules and these and the distal convoluted tubules often gave the comparative appearance of dilatation because of their normal size. The vessels were normal. Serial sections of the cortical haemorrhages did not reveal their cause. They were always peripheral and not associated with glomerular or arteriolar damage and of very recent origin. There were no signs of old haemorrhages. The renal pelves were normal.

The uterus and appendages were normal to the naked eye and the ovaries and tubes microscopically as well.

Abdomen. The stomach was normal. In the lower 50 cm of ileum some congestion of the mucosa was recognizable. The stool was dark green but no lesion was found in the colon. Microscopically sections of the ileum and ascending colon showed no signs of inflammation. The mesenteric lymph glands were normal. The liver weighed 340 g and was of average size and shape but pale. Histologically, there was some early fatty change. The gallbladder and ducts were normal. The spleen weighed 38 g. Here and in the pancreas and adrenal glands no lesion was seen, neither macroscopically nor microscopically.

Bone and Marrow. Sections of a costo-chondral junction and the right iliac crest were examined. The bone was normal and there was no significant change in the marrow.

Discussion

Chronic Acidosis. All four patients studied had a constant and striking acidosis which was only revealed by chemical investigation. None of the patients exhibited the classical air-hunger clearly enough to make the diagnosis of acidosis self-evident although dehydration was a feature in each case. A perusal of the literature reviewed at the beginning of this paper has revealed that the absence of obvious clinical manifestations of acidosis is the rule rather than the exception in this syndrome. The evidence available in the four cases does not make it possible to determine the cause of the acidosis with any degree of certainty but there is no reason to suppose that there was an abnormal production of acid substances in the plasma of our patients, nor was the intake of acid-producing substances excessive. Diarrhoea and vomiting were never so marked that chronic acidosis could have been

maintained thereby; in fact constipation was the rule. It would appear, therefore, that the source of the acidosis must be sought for in the kidneys. Acidosis in renal failure is, of course, a well-recognised and common clinical state. None of our patients, however, showed any of the features of renal (i.e. glomerular) insufficiency which would appear to be ruled out by the persistently normal ammonia-titratable acidity ratios in the first three cases, and by the histological findings in Case 4.

It is necessary, therefore, to look for some functional upset in the renal tubules. The De Toni-Fanconi syndrome is an example of a disease in which a complicated failure of tubular function is associated with chronic acidosis (McCUNE, MASON and CLARKE, 1943). None of our patients showed evidence of this disease. On the other hand, the excretion of an alkaline urine in the presence of a metabolic acidosis as occurred in our patients suggests that the tubular mechanism for the conservation of base was deficient. In Cases 1, 2 and 3, it was found that during periods of alkali treatment the urine constantly contained huge amounts of bicarbonate, although this therapy had failed to correct a persistently lowered blood carbon-dioxide level. This fact indicates that the basic cause of the acidosis was the functional inability of the tubules to reabsorb and conserve base-bicarbonate, because in normal individuals suffering from moderately severe acidosis produced by the ingestion of ammonium chloride over 99.99 per cent of the bicarbonate in the glomerular filtrate is reabsorbed by the tubules (PITTS, AYER and SCHEISS, 1949.)

The nature of the renal mechanism for the acidification of the urine and the conservation of bicarbonate is not well understood, although considerable additions to our knowledge have been made in recent years by PITTS and his co-workers (PITTS, 1945; PITTS and ALEXANDER, 1945; PITTS and LOTSPEICH, 1946; PITTS, LOTSPEICH, SCHEISS and AYER, 1948; PITTS, AYER and SCHEISS, 1949). These workers have put forward the following suggestions backed by considerable experimental evidence. No less than two-thirds and possibly as much as four-fifths or more of the fluid filtered at the glomerulus is reabsorbed during its passage through the proximal segment of the renal tubule. The residual tubular

fluid and hence the reabsorbate are essentially in osmotic equilibrium with the plasma. Only in the distal tubule does concentration or dilution of the tubular urine occur. Electrolytes are actively reabsorbed in the proximal segment and the removal of these from the tubular fluid along with other osmotically active constituents creates the diffusion force which causes the return of water to the blood-stream. It appears that the reabsorption of bicarbonate is relatively more rapid than that of water, chloride or sodium in the proximal tubule. Thus the concentration of bicarbonate in the proximal tubule falls below that in the glomerular filtrate, while the sodium level remains the same and the chloride level is higher. This preferential reabsorption of the major part of the bicarbonate in the glomerular filtrate by the proximal tubule suggests its active transport, although nothing is known of the mechanism by which this is achieved. There is evidence, moreover, that bicarbonate is reabsorbed by two dissimilar mechanisms. While the major part is absorbed by the proximal tubule, the remainder is ordinarily absorbed by the distal tubule, the process reaching completion at that level at which the urine attains its maximum acidity. The distal tubular mechanism would appear to be the same as that which converts urinary buffer salts (e.g. disodium hydrogen phosphate) into free titratable acid (e.g. monosodium dihydrogen phosphate) by exchanging hydrogen ions formed within the tubular cells for sodium ions of the urinary buffer salts. A similar exchange of hydrogen ions for bicarbonate-bound base would form carbonic acid in the urine. Since carbonic anhydrase is absent from the tubular fluid, dehydration of carbonic acid to carbon dioxide would proceed slowly and if enough carbonic acid were formed the carbon dioxide tension of the bladder urine would exceed that of the plasma. PITTS and his co-workers have shown also that bicarbonate only reaches the distal segment in appreciable quantity at plasma levels above 20 mM per litre (44.8 vols per cent) in healthy adults. Also, it is only above 26 to 28 mM per litre (58.2 to 62.7 vols. per cent) that frank excretion of bicarbonate appears in the urine. In Cases 1 and 2 large amounts of bicarbonate appeared in the urine during alkali treatment when the blood carbon dioxide content was below

35 vols. per cent. This fact strongly suggests that in our patients the tubular deficiency affected the proximal segment. The histological findings in the kidneys in Case 4 in which only the proximal convoluted tubules showed real abnormality might be taken as additional evidence to support this view. PITTS, AYER and SCHEISS (1949) have shown, further, that there is a type of competitive interference between bicarbonate reabsorption and titratable acid excretion. The presence of large amounts of bicarbonate in the distal tubule would, therefore, interfere with the production of free acid and ammonia in the distal tubule (SARTORIUS, ROEMMELT and PITTS, 1949). This might explain the finding of decreased ammonia production in adult patients by BAINES *et al.* (1945) and by ALBRIGHT *et al.* (1946). LATNER and BURNARD (1950) showed in their patients as a result of an infusion of sodium phosphate that the kidneys were, in fact, capable of secreting free acid and of increasing the output of ammonia to a degree comparable with healthy controls.

The tendency for hyperchloraemia to develop in infantile renal acidosis may also be explained by the work of PITTS, AYER and SCHEISS (1949). There exists an inverse relationship between the plasma concentrations of chloride and bicarbonate, whereby the sum of the two is relatively constant, and it seems that the renal thresholds for these two anions are inter-related in some fashion.

No information has been obtained about the possible cause or causes of the tubular deficiency in our patients. The histological appearances in Case 4 might be explicable as a congenital defect but this could hardly explain the cases which have been described in adults (ALBRIGHT *et al.*, 1940 and 1946; BOYD and STEARNS, 1942; RULE and GROLLMAN, 1944; BAINES, BARCLAY and COOKE, 1945). It may be that in some cases at least the tubular deficiency is merely the outward evidence of a more fundamental disorder which occurs elsewhere in the body, especially as in the majority of cases, in infants and adults alike, there has been no evidence of inflammatory or other primary organic disease of the kidneys themselves.

Metastatic Calcification. The presence of extensive calcification in the lungs and heart in Case 4 came as a surprise. Metastatic calcification in the presence of severe chronic renal disease has been recognised since 1855 when VIRCHOW described five cases. The following is a list of references to subsequent cases of this nature; BRYANT and HALE WHITE, 1901; SCHMIDT, 1913; HUBBARD and WENTWORTH, 1920—21; MARSDEN, 1930; LIGHTWOOD, 1932; KARELITZ and KOLOMOYZEFF, 1932; PLATT and OWEN, 1934; SMYTH and GOLDMAN, 1934; SHELLING and REMSEN, 1935; POLLACK and SIEGAL, 1935—36; MAGNUS and SCOTT, 1936; ALBRIGHT, DRAKE and SULKOVITCH, 1937; CASTLEMAN and MALLORY, 1937; HOWARD, 1938; BROWN and GINSBURG, 1940; and HERBERT, MILLER and RICHARDSON, 1941. In all of these cases renal damage was severe and glomerular insufficiency was marked. When the calcium and phosphorus blood levels had been studied they were always abnormal. Some of the patients showed severe bone disease and some of these also had marked parathyroid hyperplasia. No case similar to Case 4 has been encountered, that is, where tubular insufficiency unassociated with glomerular insufficiency was associated with metastatic calcification outside the kidneys.

In our case, a careful dissection of the neck, and the removal of part of the thyroid gland for microscopy, and a similar examination and removal of the thymus gland did not reveal the presence of any tumour. Thus, it is improbable that the calcification is associated with a parathyroid tumour. It remains to discuss the renal lesion. There was no coarse lesion in this case. Although the glomeruli have a primitive look and although an occasional glomerular fibrosis has been seen, these facts can hardly be relevant to calcification. The rare fibrosis indicates some trifling glomerular lesion, but as such, of no significance as it is not enough to account for any tubular atrophy. The tubular appearance thus commands all attention. The evenly thick basement membrane of some capsules and many proximal tubules had seemed of great importance but it was later found that such thickness has been said to be not necessarily abnormal (MAXIMOW and BLOOM, 1948). And yet, if normal, it was not present in every proximal tubule, indeed it

was more often absent, and in serial sections of control kidneys of the same age no such picture was seen. But if the basement membrane has a range of density within normal limits no range of normality is known to occur in the proximal tubular epithelium. The proximal tubules were underdeveloped and the tubular cells were smaller and flatter than normal. The conclusion of underdevelopment is reached because there is no fibrosis of significance to indicate a past severe infection or a vascular lesion. When compared to controls an even slight increase in connective tissue is apparent, a change which has been caused by reduction in the parenchymal substance. As the picture in each kidney is similar, the mild pelvic dilatation in the one is not of significance beyond further evidence of hypoplasia. From the histology it is thus inferred that there is a tubular insufficiency and possibly the lesion is congenital.

In the absence of studies of the calcium and phosphorus metabolism in our patient any attempt to correlate a tubular hypoplasia to the calcinosis must be based on hypothesis. Presumably the chronic acidosis would lead to hypercalcuria (AL-BRIGHT *et al.*, 1946) owing to mobilization of calcium from the bones to neutralize acid radicals. This would inevitably upset the normal calcium/phosphorus balance, and it is known that this may play a part in the laying down of calcium in the soft tissues (HERBERT, MILLER and RICHARDSON, 1941). None the less, it would appear that a pure tubular deficiency has not previously been reported as causing metastatic calcification, apart from nephrocalcinosis which was not present in our patient although there was very early nephrolithiasis. Pulmonary calcinosis of this type is rare at any age and at the age of our patient (fourteen months) must be almost unique. The sequence of events in the lungs is difficult to trace, but it has been demonstrated that the core of the calcified fragments is composed of elastic tissue and this must have come from the elastica of the alveolar walls and precipitation occurred on the surface of the alveolar lining cells or actually in the wall initially. It is not necessary to suggest that calcification occurred as an end result of a capillary thrombosis, as no evidence of thrombosis has been found in many

sections of the lung examined in this condition still active at the time of death. CAMERON (1930) has shown that calcification is associated with the deposit of iron, thus it is possible that the iron which has been demonstrated has followed a thrombosis with the liberation of iron therefrom. There is no thrombosis in any of the body tissues examined and it is as reasonable to suggest that a presence of previously precipitated calcium has caused sufficient irritation to the alveolar capillary for small haemorrhages and thus iron to follow the calcium as a result of the irritation. The presence of calcium in the endocardium, coronary vessels and bronchial cartilage, however, is not associated with haemorrhage. Thus it is considered that calcium was formed in or around the alveolar wall and elsewhere because of an excess in circulation.

Summary

In recent years a syndrome has been described in infants the outstanding features of which are hyperchloraemia, metabolic acidosis and often nephrocalcinosis. The literature concerning this syndrome is reviewed. Four more infants exhibiting this syndrome have been studied. The common clinical features are anorexia, failure to thrive, dehydration, severe constipation, hypotonia and a tendency to pass an alkaline urine. In three patients, detailed biochemical studies were made. These revealed chronic acidosis, a tendency to hyperchloraemia and a normal titratable acidity-ammonia ratio. During treatment with alkali, which caused marked clinical and chemical improvement, it was noted that the urine contained very large amounts of bicarbonate even in the presence of continuing acidosis. The fourth patient died. At autopsy extensive metastatic calcification was discovered affecting all the tissue elements of the lungs, the coronary vessels and the endocardium. The kidneys showed lobulation and appeared somewhat immature but there was no nephrocalcinosis. The glomeruli were not grossly abnormal. The outstanding feature was abnormality of the proximal convoluted tubules, many of which showed a marked thickening of the basement membrane and narrowing of the lumen, the lining cells of which were smaller and flatter than normal. This would appear to be the first case to be reported in which metastatic calcification (apart from nephrocalcinosis) has been described in the presence of tubular insufficiency without glomerular insufficiency. The cause of the acidosis and hyperchloraemia is discussed. It is concluded that the basic defect is an inability of the proximal tubules to conserve bicarbonate in a normal manner.

J. H. HUTCHISON et A. M. MACDONALD: *Acidose chronique chez les enfants atteints de déficience rénale tubulaire: son association avec la calcification métastatique.*

On a décrit ces dernières années, chez les enfants, un syndrome dont les signes classiques sont l'hyperchlorémie, l'acidose métabolique et souvent la néphrocalcinose. La bibliographie concernant ce syndrome est passée en revue.

Quatre nouveaux cas d'enfants présentant ce syndrome ont été étudiés. Les signes cliniques ordinaires sont l'anorexie, l'affaiblissement de l'état général, la déshydratation, une constipation sévère, l'hypotonie et une certaine tendance à avoir des urines alcalines.

Chez trois enfants on a fait des études biochimiques détaillées. Elles ont révélé une acidose chronique, une tendance à l'hyperchlorémie, et un taux d'acidité ammoniacale titrable normal. Pendant le traitement avec des alcalis, qui causèrent une amélioration marquée, clinique et chimique, il a été noté que les urines contenaient une très grande quantité de bicarbonates malgré l'acidose qui continuait.

Un des 4 malades est mort. À l'autopsie, on a trouvé une calcification étendue métastatique, touchant tous les éléments de tissu des poumons, des vaisseaux coronaires et de l'endocarde. Les reins montraient une lobulation et apparaissaient un peu immatures mais il n'y avait aucune néphrocalcinose. Les glomérules n'étaient pas grossièrement anormaux. Le signe classique était le fait que les tubes contournés étaient anormaux dans leur partie proximale. Beaucoup d'entre eux montraient un épaissement marqué de la membrane basale et une étroitesse de la lumière dont la paroi cellulaire était plus petite et plus étroite que normalement. Il semblerait que ce fût le premier cas qui ait été relaté, dans lequel la calcification métastatique (séparée de la néphrocalcinose) ait été décrite avec une insuffisance tubulaire sans insuffisance glomérulaire.

On discute la cause de l'acidose et de l'hyperchlorémie. On conclut que le défaut à la base est l'incapacité pour les tubes de conserver dans leur partie proximale les bicarbonates d'une manière normale.

J. H. HUTCHISON und A. M. MACDONALD: *Chronische Azidose bei Säuglingen infolge renaler tubulärer Insuffizienz: ihre Verbindung mit metastatischer Verkalkung.*

In den letzten Jahren ist ein Syndrom bei Säuglingen beschrieben worden, dessen hervortretende Züge Hyperchlorämie, metabolische Azidose und oft Nephrocalcinosis sind. Die Literatur über dieses Syndrom wird besprochen.

Vier weitere Kinder mit diesem Syndrom wurden studiert. Die gewöhnlichen klinischen Erscheinungen sind Anorexie, schlechtes Gedeihen, Dehydration, schwere Verstopfung, Hypotonie und Tendenz zu alkalischem Harn.

Bei drei Patienten wurden eingehende biochemische Studien gemacht. Diese ergaben chronische Azidose, eine Tendenz zu Hyperchlorämie und ein normales titrierbares Azidität-Ammoniak-Verhältnis. Während Behandlung mit Alkali, die eine merkliche klinische und chemische Besserung hervorrief, wurde festgestellt, dass der Harn sehr grosse Mengen Bikarbonat auch bei fortdauernder Azidose enthielt.

Der vierte Patient starb. Bei der Autopsie wurde extensive metastatische Verkalkung entdeckt, welche alle Gewebeelemente der Lunge, der Kranzgefässe und des Endokards betraf. Die Nieren zeigten Lobierung und schienen etwas unreif, aber es bestand keine Nephrocalcinosis. Die Glomeruli wiesen keine grobe Anomalie auf. Der hervorstechende Zug war Abnormität der proximalen gewundenen Harnkanälchen, von denen viele eine deutliche Verdickung der Basalmembran und Verengerung des Lumens zeigten, dessen Zellen (Randzellen) kleiner und flacher waren als normal. Dies dürfte der erste Fall sein, in dem metastatische Verkalkung (ausser Nephrocalcinosis) bei tubulärer Insuffizienz ohne glomeruläre Insuffizienz beschrieben worden ist.

Die Ursache der Azidose und Hyperchlorämie wird erörtert und der Schluss gezogen, dass der Grunddefekt eine Unfähigkeit der proximalen Harnkanälchen ist, Bikarbonat in normaler Weise zu behalten.

J. H. HUTCHISON y A. M. MACDONALD: *Acidosis crónica en la infancia debida a deficiencia tubular renal. Asociación con calcificaciones metastásicas.*

En los últimos años se ha descrito en la infancia un síndrome cuyas manifestaciones cardinales son: hipercloremia, acidosis metabólica y frecuentemente nefrocalcinosis. Se revisa la literatura existente sobre este síndrome. Se han estudiado cuatro niños que presentaban este síndrome. Las manifestaciones clínicas eran: anorexia, detención del crecimiento, deshidratación, constipación severa, hipotonía y tendencia a la producción de orina alcalina. En tres de los enfermos se hicieron detallados estudios bioquímicos encontrando una acidosis crónica con tendencia a la presentación de hipercloremia y una normal acidez amoniacal titulable. Durante el tratamiento con alcalinos, con los que se obtuvo una notable mejoría clínica y de laboratorio, se pudo apreciar que la orina contenía elevadas cantidades de bicarbonatos incluso en presencia de una acidosis continuada.

El cuarto paciente murió y la necropsia se halló: extensas calcificaciones metastásicas afectando a todos los elementos tisulares de los

pulmones, vasos coronarios y endocardio. Los riñones eran lobulados y algo menos desarrollados pero sin nefrocalcinosis. Los glomérulos no estaban anormalmente agrandados. Las alteraciones mas llamativas estaban en la porción proximal de los túbulos contorneados algunos de los cuales mostraban un espesamiento notable de la membrana basal y estrechez de su luz y cuyas celulas de revestimiento eran mas pequeñas y aplastadas de lo normal. Parece ser el primer caso descrito, en el cual las calcificaciones metastásicas (independientes de nefrocalcinosis) han sido asociadas a la presencia de una insuficiencia tubular sin lesión glomerular. Se discuten las causas de la acidosis e hiperloremia. Se llega a la conclusión de que existe una incapacidad de los túbulos proximales para conservar los bicarbonatos de una manera normal.

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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT NORR-
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Lower Nephron Nephrosis in Asphyxia Neonatorum

by

BENGT JONSSON

The clinical symptoms of the disease now commonly called lower nephron nephrosis were first described in 1892 by OSLER. According to MOON, ADAMI was familiar with the pathology in 1909. The frequency with which this form of renal damage occurs was not appreciated, however, until World War II when BYWATERS and BEALL in England and LUCKÉ in America reported upon its occurrence in crush injuries. Once attention had been drawn to the disease, similar renal changes were discovered in many morbid conditions, such as various forms of muscular ischemia, burns, incompatible blood transfusions, acute hemolytic anemias, septic abortions, placental hemorrhages and intoxications. Shock symptoms and/or intravascular hemolysis are characteristics of all these conditions. The picture as it is usually observed begins some hours after the injury, when oliguria or anuria and azotemia appear. As a rule, the urine contains proteins, red blood cells and casts. In cases caused by muscular damage there will be myoglobin while in destruction of the blood cells hemoglobin will be found in the urine. In spite of oliguria, the specific gravity of the urine is low. Autopsy generally discloses large, swollen kidneys with cortical pallor and a red-brown medulla. Microscopy shows focal degeneration of the tubular epithelium. The distal tubules are locally distended into small ampullae, occasionally containing pigment derivatives. Some pathologists believe that the changes are limited to the distal tubules, while others maintain that the proximal tubules are equally affected (MOON). BERGSTRAND has demonstrated an inflammatory reaction in the interstitial tissue around the degenerative foci and,

for this reason, suggests the term, tubular nephritis. In other organs edema and minor petechial hemorrhages occur.

The pathogenesis has not been entirely clarified. Several authors stress the importance of the hemoglobin and the myoglobin, and experimental investigations have shown that typical renal changes may occur when hemoglobin is injected intravenously, though only if the urine is acid. An acid hematin therefore has been supposed to exert a toxic effect on the tubular epithelium. Other studies have failed to confirm this, nor does the assumption conform entirely to clinical experiences. I have recently observed a case of acute hemolytic anemia (of Lederer's type) with a marked hemoglobinuria. The urine was acid and contained acid hematin, but no sign of renal damage was noticeable. An anoxia, due to some disturbance in the renal circulation, would seem to be the decisive factor in the origination of the renal changes. There is usually shock before the appearance of the renal symptoms. The renal circulation is exceedingly susceptible to shock and, in severe cases, the renal circulation may be greatly reduced (PHILLIPS et al.).

TRUETA's investigations of the renal circulation have in recent years caused considerable discussion. He believes that in renal ischemia there is a preferential blood flow through the juxta-medullary nephrons and that the vascularization within these nephrons is such that there may be a shunt directly from the artery to the vein. He thinks that this mechanism is of great importance in lower nephron nephrosis, especially in crush injuries. He believes that this may be brought about through a neurovascular reflex from the damaged part of the body, to the kidney or through a hormonal mechanism. The resultant decrease in renal blood flow will bring the juxta-medullary shunt mechanism into function.

Recent investigations, by MAXWELL, BREED & SMITH and CLARK, BARKER & CROSLY, have demonstrated that no such shunt mechanism can be demonstrated in man. They found that in oliguria caused by trauma or intoxication, the renal blood flow decreases. If a shunt mechanism existed, the flow should be normal. Furthermore the observed renal arteriovenous oxygen

difference increased; if a shunt had occurred, the difference should have decreased markedly. They found that extraction of PAH was normal even though the PAH clearance was markedly decreased, indicating decreased blood flow, but also indicating that the blood passing through the recovering kidney was purified in a normal manner and not "shunted" past the active renal tissue.

The probable explanations of the development of lower nephron disease are that either a prolonged and severe anoxia or some chemical agent (e.g. sulfonamides) injures the tubular epithelium. Through the damaged tubule an unselect reabsorption of the glomerular filtrate takes place, reducing the excretion and resulting in a urine of low specific gravity in spite of the decreased quantity.

At Norrtull's Hospital, during the past few years, some newborns with a severe asphyxia have been treated who have manifested symptom complexes typical of lower nephron nephrosis. Since no description of similar cases is to be found in the literature, a brief account of these cases seems desirable.

Case 1 was a male, delivered at term by mid plane forceps, for a face presentation with difficult extraction, weight 3 070 g. The pregnancy was normal, para one. The child was asphyxiated but improved after stimulation. An hour or so later his condition deteriorated. He was transferred to Norrtull's Hospital. Examination there showed him to be asphyxiated, pale-grey and somewhat cyanotic but otherwise nothing remarkable.

With continuous oxygen therapy, he remained practically unchanged for the first 5 days. He was fed by tube and vomited considerably requiring some parenteral fluids. The widely fluctuating body weight indicated a disturbed fluid equilibrium. The amount and frequency of urination was not recorded, but the urine contained proteins, occasional red blood cells and casts. On the 3rd day the NPN was 90 mg%. No icterus or anemia was noted.

After the 5th day he improved rapidly. The colour became normal, the general condition satisfactory, the urinary changes disappeared and the NPN decreased. His recovery was complete and was followed by normal growth and development, without evidence of residual renal or cerebral damage.

Case 2 was a well developed male, weight 3 130 g. The mother, a para one, was healthy during the pregnancy but at delivery had slight

hypertension without albuminuria. The labour and delivery were normal. The liquor amnii was strongly mixed with meconium. The child was extremely asphyxiated at birth. A great deal of pharyngeal mucus and meconium had been aspirated. He improved somewhat after artificial respiration and stimulants, but respiration was never normal. He was admitted to Norrtull's Hospital 10 hours after birth. He was still asphyxiated with slight cyanosis, severe dyspnea and with deep, thoracic contractions at every inspiration. Two hours later he began to have generalized clonic spasms; repeated twice daily thereafter. His condition deteriorated during the following days, the cyanosis increased and he had repeated attacks of respiratory arrest. He was given oxygen and was tube fed.

He did not void during the first 72 hours. On the fourth day of life, a little urine was passed, free of proteins or blood cells. The NPN was 127 mg%, the alkali reserve 35.8 vol%, the blood chlorides 292 mg%, the Hb 20.8 g%, and the red blood cells 5.68 millions/cmm. He was never jaundiced. Parenteral fluids in the form of 1.3 % of bicarbonate and 5 % of glucose were given and resulted in the appearance of edema. He continued to void only very small amounts. He died on the 6th day.

Autopsy disclosed complete pulmonary atelectasis except small areas of the right lung. There was cerebral congestion with pinpoint hemorrhages of the temporal lobes. The liver appeared normal except for a 3 cm rounded area of necrosis. The kidneys were pale, and together weighed 23 g. The pyramids were a reddish brown, and the pale parenchyma bulged over the cut surface.

Microscopic examination performed by dr. A. Bergstrand revealed: "There were in the cerebrum, chiefly around the small arteries and capillaries, numerous minor hemorrhages. Small, fresh fibrinous thrombi were noted in many places, in connection with necrosis of the vascular walls. No specific vascular changes were observed.

In the liver about the major area of necrosis and close to it, there were a number of microscopic areas of necrosis. In the necrotic liver tissue small fibrinous thrombi were noticeable in many places in remnants of capillaries. The liver tissue also contained a profuse amount of ferrous pigment, mainly stored in the liver cells, but also, in Kupffer's cells.

There were no definite changes in the renal glomeruli. Nor was there any degeneration or desquamation of the tubular epithelium. The proximal tubules were free of pigment but there were, on the other hand, numerous casts of a peculiar yellowish brown, with traces of hemoglobin, in the distal convoluted tubules and in the collecting tubules.

The histologic examination, therefore, reveals a capillary damage in liver and cerebrum with necrosis in the vascular walls, fibrinous thrombi and perivascular hemorrhages and necrosis in the surrounding tissue, an increased destruction of the blood cells with storage of ferrous pigment

in the liver, and renal changes which are usually termed distal tubular nephritis."

Case 3 was a well developed female child, weight 3 050 g. The mother, a para one, was healthy during the pregnancy, but had a narrow pelvis. Though the labour lasted 12 hours, the delivery was not considered difficult. The child was, however, deeply asphyxiated. She was treated at the obstetric hospital during the first 72 hours. On the 3rd day, she had a general clonic convulsion and was transferred to Norrtull's Hospital.

Examination revealed a stuporous, moderately cyanotic infant with a faint cry but no other sign of intracranial injury or other physical abnormalities. Her condition deteriorated during the following days. There was increasing stupor, the skin became cold and pale grey. There was no pricking reaction. The fontanel grew tense but lumbar puncture revealed nothing abnormal. On the 5th day of life, she was completely relaxed and unresponsive. Palpation of the relaxed abdomen disclosed two firm masses in the costovertebral areas; interpreted as enlarged kidneys. The exact amounts of the scanty urine could not be determined. The urine contained protein but no red blood cells. The NPN was 92 mg%, blood chlorides 341 mg%, alkali reserve 22.4 vol%. Hb. 20.8 g%, red blood cells 6.12 millions/cmm. During the 3rd—5th days of life, the patient had a slight icterus. Her blood group was A Rh (+); her mother's A₁Rh (+). The mother's blood was free of irregular agglutinin. A Coomb's test on the child's blood was negative. The child was fed by tube and was given oxygen continuously. No parenteral fluid was given. She vomited a little. On the 8th day, urination increased while the NPN decreased. She then improved very rapidly. Later there were no signs of renal damage and the kidneys appeared normal by intravenous urography. However she displayed signs of encephalopathy with convulsions and retarded development.

Discussion

The above 3 cases showed a similar clinical picture. They had severe asphyxia and, during the first week of life, signs of renal insufficiency with a rise in NPN of 90 to 127 mg%. Cases 2 and 3 had oliguria and the urine volume was not noted in Case 1. One child died, revealing, at the autopsy, capillary damages with minute perivascular hemorrhages in several organs, as is not unusual in asphyxia. The distal renal tubules showed numerous casts containing hemoglobin, of the type found in lower nephron nephrosis, yet there was no demonstrable epithelial degeneration.

Pathologically there was a suggestion of severe blood destruction, but, clinically no signs of increased hemolysis were noticed.

In asphyxia neonatorum there is not only a respiratory insufficiency but also a circulatory insufficiency with more or less pronounced symptoms of shock. In each of these 3 cases, pronounced shock symptoms were found. This provides a likely explanation for the origination of the renal damage. The cause of the asphyxia may be variable. Case 1 had, no doubt, some intracranial injury. Case 2 had poor thoracic function and almost total atelectasis. Case 3 had severe intracranial damage with residual manifestation which may have been in part the result of the asphyxia.

The reason why such renal lesions have not been described in newborns may be due to a failure to look for the process. But, apart from that, an exceedingly severe asphyxia must be required to produce such damage, and the great majority of such severe cases die, from the asphyxia, too early to allow the renal lesions and symptoms to develop.

The first aim of the therapy in these cases should be to eliminate the asphyxia. Severe cerebral damage offers a poor prospect and treatment therefore purposeless. However, it is often impossible to decide in the early phase whether or not irreversible cerebral damage exists. Oxygen therapy is, of course, imperative. Also, if anemia is contributing to the anoxia it should be corrected by transfusions. It is of interest to note that lower nephron nephrosis has, during the previous year, been successfully treated with exchange transfusions (DUSSET and SNAPPER).

The renal damage being reversible, it is important to manage the patient to his best advantage from the viewpoint of his uremic condition. The fluid and electrolyte equilibrium must be controlled. This offers technical difficulties in newborns, but by checking the body weight, a fair conception of the fluid equilibrium can be arrived at. The administration of fluids must not be increased with a view of forcing the renal barrier, since this will result only in the development of edema, as is evident from Case 1. It is necessary to limit fluids and electrolytes to the amounts voided and that lost by respiration and insensible perspiration while

there is oliguria. A hypertonic glucose solution is useful, if given cautiously, in maintaining some food intake. When the diuresis begins, the excreted quantity of fluid and electrolytes is replaced.

Summary

A brief account is given of lower nephron nephrosis in 3 cases of severe neonatal asphyxia. The etiology of the renal lesion is discussed.

B. JONSSON: *Néphrite tubulaire dans l'asphyxie des nouveaux-nés.*

Un bref compte-rendu nous parvient sur 3 cas d'asphyxie grave du nouveau-né présentant une néphrose de la partie inférieure du néphron. L'étiologie de la lésion rénale est discutée.

B. JONSSON: *Untere Nephron-Nephrose bei Asphyxie Neugeborener.*

Der Verfasser berichtet kurz über untere Nephron-Nephrose in drei Fällen schwerer neonataler Asphyxie. Die Ätiologie der renalen Läsion wird besprochen.

B. JONSSON: *Nefrosis de la porción tubular inferior en la asfixia del recién nacido.*

Se hace una sucinta revisión sobre tres casos de nefrosis de la porción tubular inferior en recién nacidos con asfixia severa. Se discute la etiología de la lesión renal.

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Beiträge zur Nierenpathologie¹

von

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Zum besseren Verständnis der nachfolgenden Ausführungen seien einige Angaben über die moderne Anschauung der *Anatomie und Physiologie des Nephrons* gegeben.

In den Kapillaren des *Glomerulums* wird proportional der sie durchfließenden Blutmenge ein nahezu eiweissfreies, dem Plasma isotonisches Ultrafiltrat, der Primärharn, in den Hohlraum der Bowmanschen Kapsel gepresst.

Im *proximalen Abschnitt des Tubulus* (Hauptstück) werden einerseits die Glucose, der grösste Teil der Phosphate, die Aminosäuren und andere wertvolle Substanzen rückresorbiert und zwar ohne Änderung der Wasserstoffionenkonzentration und des osmotischen Druckes des Glomerulumfiltrates, anderseits hochmolekulare, etwa körperfremde Substanzen ausgeschieden wie z.B. das an Eiweiss gebundene Diodrast und vielleicht auch körperfremd gewordene Plasmaproteine, z.B. gewisse Lipoglobuline beim Nephrosesyndrom. Sowohl bei der selektiven Rückresorption als auch bei der Sekretion im proximalen Tubulusabschnitt sind enzymatische Prozesse am Werke.

Die Rückresorption der Hauptelektrolyte der extrazellulären Flüssigkeit Na und Cl und mit ihnen eines guten Teiles des Wassers erfolgt sowohl im proximalen als auch im distalen Tubulus; in letzterem jedoch geht die Rückresorption des Na und des Cl fakultativ entsprechend den Bedürfnissen des Gesamtorganismus, d.h. unter der Kontrolle der Hormone und des Nervensystems vor sich.

Im *distalen Tubulus* wird das Säurebasen-Gleichgewicht des Organismus reguliert. Der Säureäquivalenten entledigen sich die Nieren

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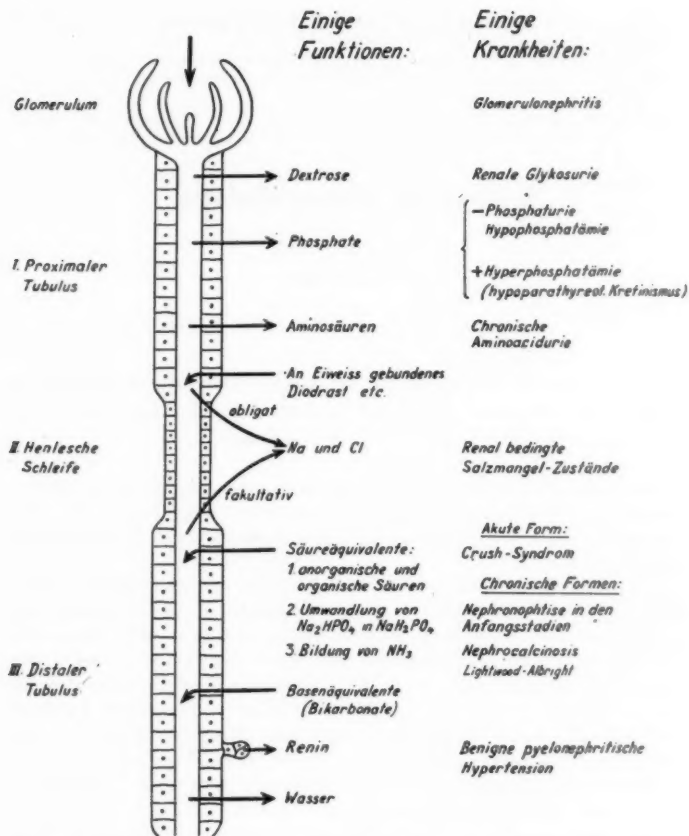
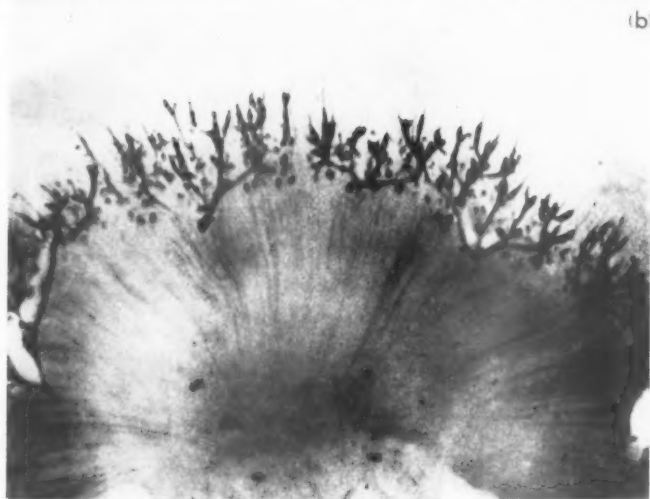


Abb. 1. Schematische Darstellung des Nephrons, seiner Partialfunktionen und der entsprechenden Krankheiten.

erstens durch Verschiebung der Wasserstoffionen-Konzentration des Urins gegen die saure Seite hin, die bei gesunden Nieren bis zum PH von 4,8 gehen kann. Schon bei einem PH von 6,0 wird das im Blut zu 80 % als basisches (NaH_2HPO_4) enthaltene Phosphat zu 90 % als saures Salz (NaH_2PO_4) ausgeschieden, ferner ca. 20 % der organischen Säuren als freie Säuren. Dank der Pufferwirkung der Phosphate und der organischen Säuren ist das Säurebindungsvermögen (Titrations-



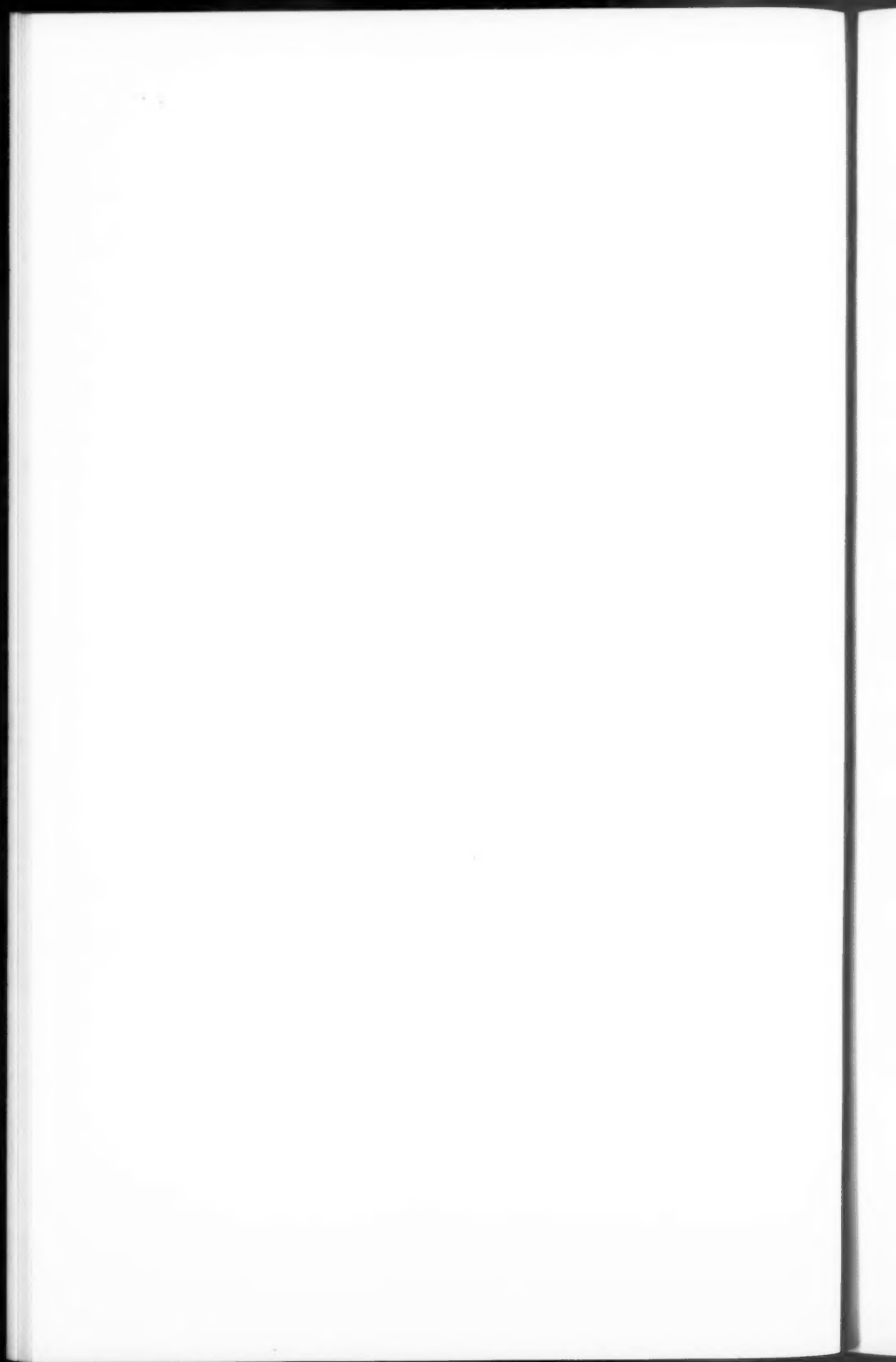
(a)



(b)

Abb. 2. Röntgenmikrophotographie von Schnitten der linken und rechten Niere eines Kaninchens (aus Trueta, *Studies of the renal circulation*).

- a) Die rechte nicht gereizte Niere; das mit dem Kontrastmittel sichtbare Blut füllt hauptsächlich die interlobulären Arterien und die Glomerula der Rinde.
- b) Der periarterielle Nervenplexus der linken Nierenarterie ist faradisch gereizt worden. Dadurch ist das Blut von der Rinde durch den Kurzschluss der juxtamedullären Gefäße abgeleitet worden. Die interlobulären Gefäße und Glomerula sowie die Arteriae medullares rectae sind stark dilatiert.



azidität oder Säureüberschuss), mit andern Worten die Basenökonomie eines sauren Urins sehr gross; deswegen bleibt bei einer Hyperphosphaturie das PH des Urins nahe beim PH des Blutes, auch wenn viele Säureäquivalente ausgeschieden werden. *Zweitens* wird das Anion HCO_3 rückresorbiert und als Kohlensäure in den Lungen ausgeschieden. *Drittens* vermag die gesunde Niere aus Aminosäuren auf Kosten des neutralen Harnstoffes die Base Ammoniak zu bilden. Dank all dieser Mechanismen ist die gesunde Niere in der Lage, auch beim Vorliegen einer Acidose die wertvollen anorganischen Basen Natrium, Kalium und Calcium einzusparen.

Überschüssige Basenäquivalente werden eliminiert erstens durch die Verschiebung des PH gegen die basische Seite hin und zweitens dadurch, dass das Anion Bicarbonat (HCO_3) in vermehrter Masse in den Harn ausgeschieden wird.

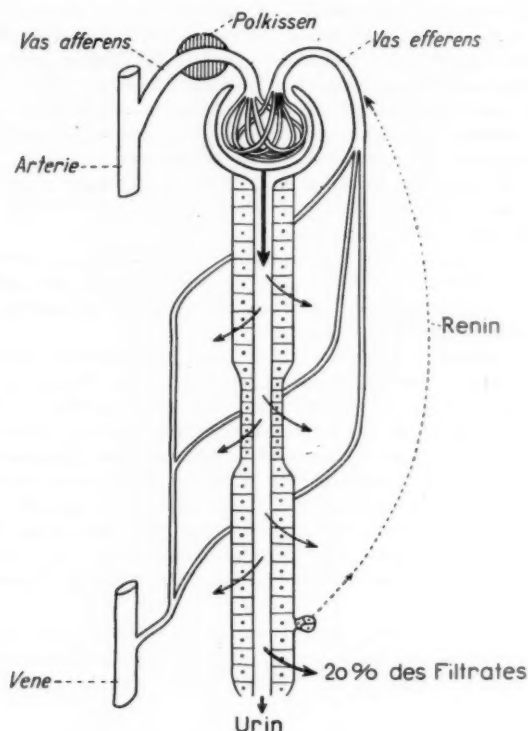
Die definitive Eindickung des Urins geht wohl zu unterst im Nephron vor sich und zwar dadurch, dass dasjenige Wasser (ca. 20 % des Glomerulumfiltrates), das bei der Passage durch den Tubulus noch nicht rückresorbiert wurde, diesen ebenfalls verlässt. Diese terminale Eindickung erfordert wahrscheinlich den grössten Energieaufwand.

Die selektive Rückresorption wichtiger Stoffe wird reguliert durch eine Reihe von Hormonen und überwacht durch spezielle Stoffwechselzentren im Zentralnervensystem: so fördert das Hormon des Hypophysenhinterlappens die Wasserrückresorption, das Nebennierenrindenhormon die des Na und Cl, das Parathormon hemmt die der Phosphate usw.

Die *Blutversorgung der Nieren*, welche 1/4 des aus dem Herzen strömenden Blutes beansprucht, obwohl das Gewicht beider Nieren kaum 1/100 desjenigen des Körpers beträgt, wird durch 3 Mechanismen reguliert:

1. Je nach dem Quellungszustand des Polkissens, — das ist eine Manchette myoepithelialer Zellen um das Vas afferens — wird die Blutzufuhr zum Glomerulum geregelt; bei hohem Blutdruck verengt sich das Vas afferens, wodurch das zarte Glomerulum vor einer Überfüllung bewahrt wird. Diese Art der Durchblutungsregelung nennen PAGE und CORCORAN die *neurogene*.

2. Durch Verengung des Vas efferens kann der Druck im Glomerulum erhöht werden, was eine prozentuale Vermehrung des Ultrafiltrates in Bezug auf die durchfliessende Blutmenge zur Folge hat. Diese Art der Regelung nennen PAGE und CORCORAN die „humoral renal pressor activity“ und verstehen darunter die Wirkung des *Renins*, des Inkretes der Niere, welches im distalen Tubulusabschnitt und zwar in besonderen Zellknospen gebildet und durch den Reninaktivator aus der Leber in das kreislaufaktive Hypertensin umgewandelt wird (HOUSLEY). Je geringer die Durchblutungsmenge, desto grösser die Renin-



Glomeruläre Filtration	125	} cm ³ /Minute
Tubuläre { Sekretion	0	
{ Rückresorption	124	
Clearance	1	

Abb. 3. Schematische Darstellung der Regulationen 1 und 2 (siehe Text) der Blutversorgung des Nephrons sowie der Ausscheidung des Wassers. Von 125 ccm Wasser, die im Glomerulum ausgepresst werden, werden ca. 80 % im proximalen Tubulus, in der Henle'schen Schleife und im proximalen Teil des distalen Tubulus „obligat“, das heisst als Lösungsmittel von Kristalloiden rückresorbiert. 20 % gelangen zuunterst im distalen Tubulus „fakultativ“ zur Resorption, das heisst entsprechend den Bedürfnissen des Gesamtorganismus unter dem Einfluss des Adiuretins. Weniger als ein Hundertstel des im Glomerulum filtrierten Wassers wird als Urin ausgeschieden.

produktion, desto mehr Ultrafiltrat wird aus der gleichen, das Glomerulum durchströmenden Blutmenge ausgepresst. Am grössten ist die Reninproduktion bei der Ischämie. Bewiesen wurde dies durch den berühmten GOLDBLATT-Versuch, wonach es regelmässig zu einer Zunahme des Renins und zur Hypertension kommt, wenn die Nierenarterie partiell zugeklemmt wird. Wir werden am Schlusse unseres Vortrages die Hypothese aufstellen, dass ausser der Ischämie auch ein lokaler entzündlicher Reiz zur Mehrproduktion von Renin führen kann; diese Hypothese gibt eine plausible Erklärung für die benigne pyelitische Hypertension.

3. Schliesslich kann der Blutzufluss in die Rindenregion durch den *juxtamedullären Kreislauf* (auch kleiner Nierenkreislauf genannt) reguliert werden. Dieser hat nach TRUETA eine Kurzschlussfunktion und verhindert gegebenenfalls eine Überflutung der Rinde, indem er das Blut durch arteriovenöse Anastomosen der geraden Markgefässe abfliessen lässt. Der Kurzschluss kann experimentell herbeigeführt werden, wenn das periarterielle Nervengeflecht um die Arteria renalis gereizt wird (Abb. 2), ferner tritt er in Funktion, wenn das Blut mit Giftstoffen beladen ist, welche den empfindlichen Glomerulumapparat schädigen könnten. Auch bei Stauungszuständen, vielleicht um eine Stase in der Rindenregion hintanzuhalten und damit eine genügende Zirkulation in diesem wichtigen Nierenteil zu ermöglichen, sind besonders die Gefässe des juxtamedullären Kreislaufes stark dilatiert; deswegen erscheint oft bei der Autopsie sowohl bei Stauungszuständen als auch bei Intoxikationen die Gegend zwischen Rinde und Mark als ein mehrere Millimeter breiter blauroter Streifen.

Man kann die Nierenerkrankungen je nach dem Ort der Läsion einteilen in Affektionen des Glomerulum, des proximalen und des distalen Tubulus.

Affektionen des Glomerulum

Prototyp ist die akute hämorrhagische Glomerulonephritis, welche nach den schönen Untersuchungen von MASUGHI meist allergischer Natur ist. Die *Symptome* der Glomerulonephritis lassen sich folgendermassen zusammenfassen:

1. Symptome bedingt durch die pathologisch *gesteigerte Durchlässigkeit* des Glomerulums
 - a) Proteinurie
 - b) Hämaturie

2. Symptome bedingt durch die *Behinderung der Glomerulumdurchblutung und der Auspressung des Ultrafiltrates:*

- a) Oligurie bis zur Anurie
- b) Retention: α) von Schlackenstoffen des Eiweissstoffwechsels
 β) von Phosphaten, Sulfaten usw.
 γ) der Elektrolyten Na und Cl (Hyperelektrolytämie)
 δ) des Wassers (Oedeme)
- c) Hypertension infolge Reninüberproduktion

3. *Komplikationen:*

- a) *Echte oder stille Urämie* infolge der massiven Retention der harnfähigen Stoffe
- b) *Eklamptische Pseudourämie* bedingt durch
 - α) Hirnoedem infolge der Hyperelektrolytämie
 - β) Hypoxämie des Gehirns infolge von Gefäßkrämpfen bei der Hypertension
 - γ) Hypocalcämie als Reaktion auf die Hyperphosphatämie, sowie infolge des Basenverlustes bei Acidosis

Als Beispiel sei die Kurve eines 6 jährigen Mädchens wiedergegeben (Abb. 4), welche akut an einer hämorrhagischen Nephritis erkrankte und innerhalb weniger Wochen vollständig ausheilte. Als Zeichen der pathologischen Durchlässigkeit der Glomerula bestand eine ausgesprochene Proteinurie und eine sichtbare Hämaturie; als Zeichen der Behinderung der Glomerulumdurchblutung eine Retention von RestN und Phosphaten, Oligurie und Blutdruckerhöhung. Die niedrige Alkalireserve ist eine Folge der Anhäufung retinierter Säuren im Blute. Die Hyposalämie in den ersten Tagen ist wohl eine Folge des NaCl-Verlustes durch das Erbrechen. Bereits nach wenigen Tagen, wie das Erbrechen sistiert, macht die Hyposalämie der zu erwartenden Retentionshypersalämie Platz (Abb. 5).

Die Behandlung der akuten Glomerulonephritis besteht darin, dass man während einigen Tagen nur 500—700 ccm einer 10 % Zuckerlösung und dann während einigen Wochen eine eiweiss-, salz- und eher wasserarme Schondiät verabreicht. Bis vor 1 1/2 Jahrzehnten pflegten wir im Kinderspital und mit uns

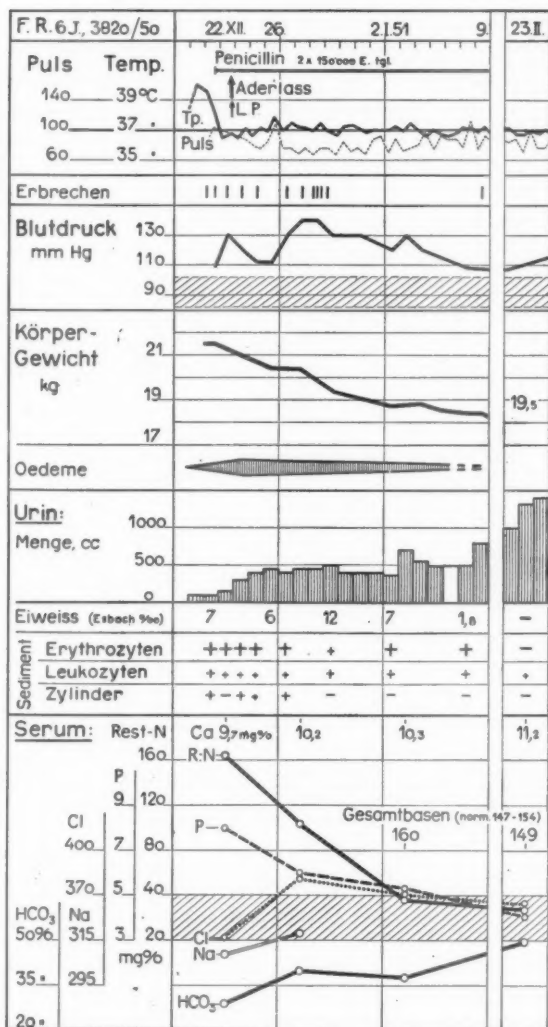


Abb. 4. Übersichtskurve des Verlaufes einer typischen „allergischen“ diffusen Glomerulonephritis mit allen Folgen der passageren Behinderung der Glomerulardurchblutung.

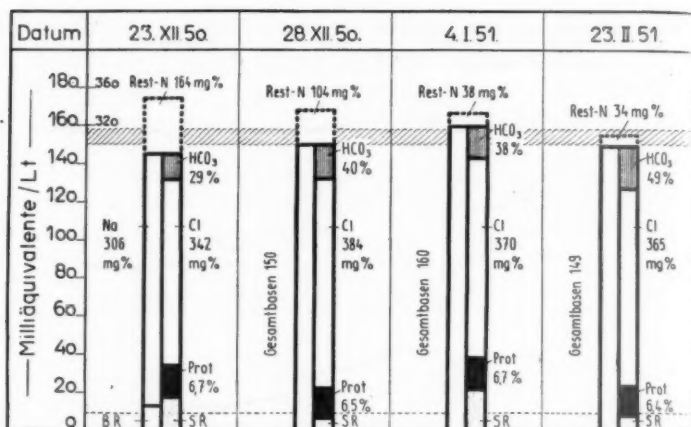


Abb. 5. Ionogramm bei einer akuten diffusen Glomerulonephritis mit initialer Hyperelektrolytämie. Die durch das heftige Erbrechen bedingte Hyposalämie verhindert ein zu starkes Ansteigen des osmotischen Druckes in der extrazellulären Flüssigkeit.

wohl die meisten Kinderärzte in Verallgemeinerung der guten Erfahrungen bei der Glomerulonephritis nahezu sämtliche Nephropathien eiweiss- und salzarm zu ernähren. Heute wissen wir, dass dies nicht nur überflüssig, sondern sogar gefährlich ist; bei der Lipoidnephrose ist nach heutigen Erkenntnissen eine eiweissreiche Diät am Platz und wir werden unten sehen, dass bei manchen Nephropathien des distalen Tubulus, welche mit einem Diabetes salinus renalis einhergehen, die Einschränkung des Kochsalzes lebensgefährlich werden kann.

Die Affektionen des proximalen Tubulusabschnittes

Die Affektionen des proximalen Tubulusabschnittes erkennt man hauptsächlich an der gestörten Rückresorption der Dextrose, der Aminosäuren und der Phosphate (Ab. 1). Da die Glykose und die Aminosäuren beim Gesunden restlos rückresorbiert werden, kann sich die Krankheit nur in einer mangelhaften Resorption manifestieren, d. h. in Form der renalen

Glykosurie und Aminoacidurie. Die proximale Rückresorption ist ein fermentativer Vorgang; Phosphorylasen, welche Phosphorsäure an organische Verbindungen anlagern, und Phosphatasen, welche umgekehrt Phosphorsäure aus Estern frei machen, sind dabei im Spiele. STOWERS, DENT und CAMERON konnten in einem Falle chronischer Aminoacidurie mit Hilfe der Phosphatasefärbung nach Gomori tatsächlich ein Fehlen der Phosphatase in den proximalen Tubuli nachweisen. Eine Störung der Phosphatrückresorption kann sich dagegen sowohl in Form einer zu geringen als auch einer zu intensiven Aktivität äussern. Eine zu geringe Rückresorption wird zur Hyperphosphaturie und Hypophosphatämie führen, z. B. zum Krankheitsbilde der familiären chronischen Hyperphosphaturie (Phosphatdiabetes) mit Hypophosphatämie und D-Vitamin-resistenter Rachitis (FANCONI), eine zu starke zur Hyperphosphatämie z. B. zur Pseudohypoparathyreose ALBRIGHT.

Ein schönes Beispiel einer gehemmten Rückresorption der Glykose, der Aminosäuren und der Phosphate habe ich mit BICKEL ausführlich publiziert:

Der 4 jährige Bub (J. N. 4955/47) dessen Urgrossväter Geschwister waren, zeigt folgende Symptome: Zwergwuchs (76 cm), mächtig vergrösserte glykogenotische Leber, Thermolabilität. Im meist alkalisch oder neutral reagierenden (pH 6,8—8,0), durch Phosphate und Carbonate getrübten Urin gelegentlich Spur Albumen, Glykosurie bis 50 gr pro die. Chromatographisch und mit der Formoltitration nachgewiesene intensive Aminoacidurie und eine meist auch sichtbare Phosphaturie von durchschnittlich 55,4 mg (bis 65,5 mg) pro die und kg (normale Kontrollkinder durchschnittlich 30 mg). Der NH_3 -Koeffizient hoch (9 statt 2—3, maximum 13) als Zeichen, dass die NH_3 -Produktion des distalen Tubulus in keiner Weise gestört war. Die Isosthenurie mag z. T. durch die mangelhafte Wasserrückresorption im proximalen Tubulus sowie durch die Glykosurie bedingt sein (der hohe Zuckergehalt des Urins hält Wasser zurück!) und braucht nicht ohne weiteres auf einer Mitschädigung der Henle'schen Schleife und des distalen Tubulus zu beruhen. Die meist alkalische oder neutrale Reaktion lässt sich am besten durch die Pufferwirkung der reichlich ausgeschiedenen Phosphate erklären. Im Blute Hypoglykämie, Hypophosphatämie, wahrscheinlich auch Hypoaminoacidurie, RestN dagegen normal, Phosphatase und Alkalireserve vermindert, Cholesterin vermehrt.

Es ist dies ein Prototyp einer upper nephron nephrosis, einer Nephropathie des proximalen Tubulus. Die fermentative Störung bleibt nicht immer nur aus den proximalen Tubulus beschränkt, so deutet z. B. die mächtige Glykogenspeicherung in der Leber auf eine Störung der Glykogenolyse hin, an der auch Phosphorylierungsprozesse beteiligt sind. In analoger Weise ist die chronische Aminoacidurie häufig mit einer *Cystinosis* kombiniert, wobei man besonders leicht die doppelbrechenden Cystinkristalle im Knochenmarksausstrich und durch sie bedingte Cornealtrübungen nachweisen kann. Die Cystinose deutet darauf hin, dass auch der intermediäre Stoffwechsel mit den Aminosäuren nicht fertig wird, sodass die am schwersten lösliche, das Cystin, in amorpher oder kristallinischer Form vor allem im reticuloendothelialen System abgelagert wird. Im oben zitierten Falle gelang es uns jedoch nie, weder im Knochenmark noch in der Cornea Cystin zu finden, sodass wohl eine auf den proximalen Tubulus beschränkte rein renale Störung des Aminosäurestoffwechsels vorliegen dürfte.

Auch bei zwei Brüdern, die an einer *Oligophrenia phenylpyruvica* litten, gelang uns der Nachweis einer ausgiebigen Aminoacidurie. Dieser 1934 von FÖLLING entdeckten rezessiv vererbaren Krankheit liegt demnach nicht nur eine Störung des Abbaues der Phenylbrenztraubensäure, sondern auch eine Störung der Aminosäureverarbeitung, speziell der tubulären Rückresorption zu Grunde. Nicht nur im Urin, auch im Liquor gelang es uns, einen vermehrten Gehalt an Phenylalanin nachzuweisen.

Wie bereits gesagt, kann bei den *Phosphaten* die Störung nicht nur in einer Verminderung, sondern auch in einer Verstärkung der Resorption liegen, was eine dauernde Hyperphosphatämie zur Folge hat. Diese ihrerseits führt eine Hypocalcämie herbei, wodurch die Bedingungen für die Entstehung einer Tetanie gegeben sind. Die Rückresorption von Phosphaten wird in erster Linie vom Parathyreoideahormon gehemmt, daher wird bei der Hypoparathyreose zu viel Phosphat rückresorbiert. Nun hat ALBRIGHT mit dem Ellsworth—Howard-Phosphaturie-Test zeigen können, dass es Individuen gibt, bei denen die Nierentubuli auf das Parathyreoideahormon nicht ansprechen (non

response). ALBRIGHT spricht von *Pseudohypoparathyreose*. Das Krankheitsbild ist durch die Neigung zu tetanischen Krämpfen, ausserdem durch Kleinwuchs, unersetzten Körperbau, rundes, volles Gesicht, kurze Metacarpalia, Pachydermie und leichte Oligophrenie gekennzeichnet. Eine anatomische Grundlage für dieses Nichtansprechen der Nierentubuli hat man allerdings bis heute noch nicht gefunden. Es ist nicht ausgeschlossen, dass die wesentliche Störung gar nicht in den Nierentubuli, sondern an einem übergeordneten Ort, etwa im Zentralnervensystem liegt. Sowohl SCHÜPBACH und COURVOISIER, als auch ZELLWEGER und GIRARDET konnten zeigen, dass bei einem der Pseudohypoparathyreose analogen Krankheitsbild der Ellsworth-Howard-Test positiv ausfällt, also die Nierentubuli auf das Parathyreoideahormon gut ansprechen, während die übrigen Symptome unbeeinflusst bleiben. Den Fall von ZELLWEGER und GIRARDET hatte FANCONI schon 1945 als chronische Hypocalcämie mit rezidivierender Tetanie im Säuglingsalter beschrieben und die Ursache in einer Störung der zentralnervösen Regulation gesucht. Der Vorschlag SCHÜPBACHS, alle diese Fälle unter dem Namen *hypoparathyreotischer Kretinismus* zusammenzufassen, scheint durchaus berechtigt zu sein.

Affektionen, die die Elektrolytrückresorption betreffen

Leidet die Rückresorption der Elektrolyte, so können leicht Salz-mangelzustände eintreten. Die Einregulierung der Elektrolyte Na^+ und Cl^- ist weitgehend, aber nicht durchwegs mit der Einregulierung des Wassers gekoppelt. Beide Prozesse werden, und zwar im distalen Tubulus, hormonal gesteuert: das Adiuretin des Hypophysenhinterlappens fördert die Rückresorption von Wasser, das Nebennierenrindenhormon diejenige von Na^+ und Cl^- . Die Einregulierung des NaCl -Stoffwechsels kann auch rein renal gestört sein; einerseits kann es bei Vorliegen eines glomerulären Passagehindernisses zu einer Salzstauung je nach dem Stand des Wasserhaushaltes mit oder ohne Hyper Elektrolytämie kommen, andererseits kann die tubuläre Rückresorption insuffizient werden. Ich habe 1937 und 1938 für diese Insuffizienz

den Namen *Diabetes salinus renalis* vorgeschlagen; im angelsächsischen Schrifttum spricht man auch von *salt losing nephritis*. Der Diabetes salinus renalis kommt hauptsächlich bei gewissen Formen der Schrumpfniere (z.B. bei der hyperphosphatämischen renalen Rachitis, bei hydronephrotischen Nieren usw.) vor. Werden solche Kinder NaCl-arm ernährt, so kann die NaCl-Ausscheidung durch die Nieren nicht wie normaliter durch eine ausgiebige Herabsetzung der NaCl-Konzentration sondern hauptsächlich durch eine Verminderung der Urinmenge etwas eingeschränkt werden. Dies ist aber ein zweischneidiges Schwert, denn dadurch wird auch die Ausscheidung von Stoffwechselschlacken usw. erschwert, der RestN, die Phosphate usw. nehmen im Blut zu. Übrigens reicht die Verminderung der Urinmenge meistens nicht aus, um einen Salz-mangelzustand hintanzuhalten (Abb. 6).

Die Erkenntnis, dass bei gewissen meist chronischen Nierenerkrankungen die Fähigkeit, NaCl rückzuresorbieren, gelitten hat und damit die Gefahr des Salz-mangelzustandes bei zu salzarmer Kost oder bei starken extrarenalen Salzverlusten, etwa bei Erbrechen, Durchfällen und profusen Schweissen, gross ist, hat im Kinderspital Zürich manches Kind von einer schweren „Urämie“ durch die Zufuhr von Kochsalz prompt geheilt und z.B. Kindern mit doppelseitiger Hydronephrose nicht nur für einige Monate, sondern für Jahre das Leben verlängert. Die Gefahr des bedrohlichen Salz-mangelzustandes ist dann besonders gross, wenn die glomeruläre Ultrafiltration noch intakt ist, sodass grosse Mengen von NaCl-Ionen in das Ultrafiltrat gelangen und nicht wieder rückresorbiert werden können, also bei Nephropathien des distalen Tubulus. Ist das Glomerulum erkrankt, so wird die dadurch bedingte NaCl-Retention (s. Seite 414) dem Salzverlust durch tubuläre Insuffizienz entgegenarbeiten. Dies erklärt, warum ich in meiner langen Praxis erst einen Fall von „Salz-mangelurämie“ im Verlaufe einer akuten Glomerulonephritis, und zwar bei einem Scharlachpatienten, erlebt habe.

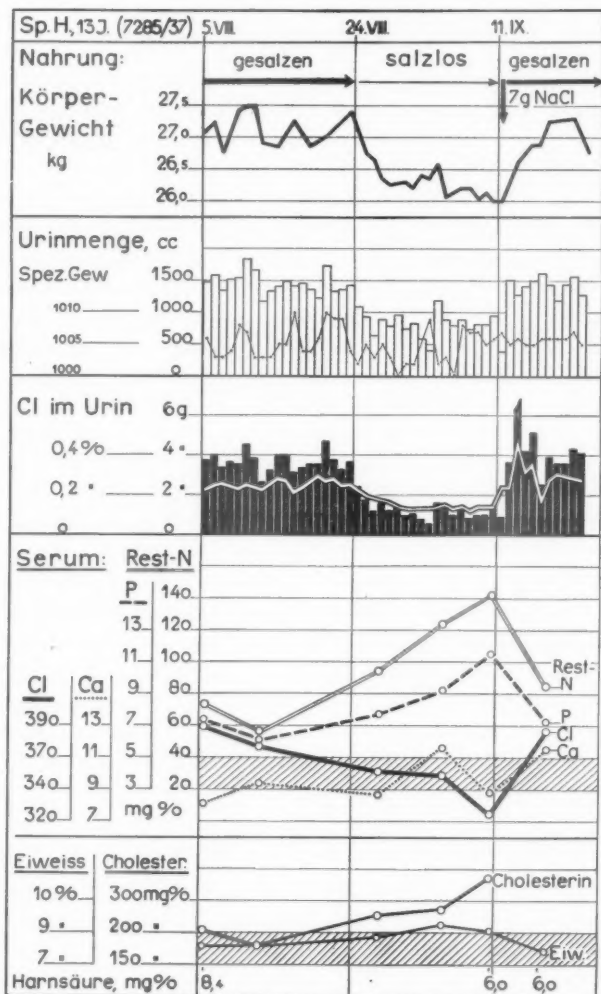


Abb. 6. Wirkung der kochsalzfreien Diät bei einem 12 jährigen Patienten, der an einer hyperphosphatämischen renalen Rachitis und an Diabetes salinus renalis leidet. Sturz des Serum-Chlors, weil die Nieren nicht in der Lage sind, das Salz „fakultativ“, d. h. entsprechend den Bedürfnissen des Gesamtorganismus zu retinieren. Die procentuale Cl-Ausscheidung (weisse Linie) nimmt nur wenig ab.

Affektionen des distalen Tubulusabschnittes

Gar nicht so selten kommt es zu Affektionen des distalen Tubulusapparates (*lower nephron nephrosis*). Im Gegensatz zum proximalen ist der distale Tubulus exogenen Schädigungen sehr zugänglich und zwar aus folgenden Gründen:

1. Im distalen Tubulusabschnitt wird der Harn stark eingedickt, und damit nimmt die Konzentration gefährlicher Stoffe stark zu. Es kommt leicht zur massigen Präzipitation von körperfremden Stoffen wie Sulfonamiden, oder von körperfremd gewordenen Stoffen (Methaemoglobin, Myoglobin usw.), was ein *Crush Syndrom* auslösen kann. Gelegentlich sind es Calciumsalze, die gefällt werden, wenn eine Hypercalcämie besteht oder wenn etwa bei einer renalen Acidosis die Tubulusepithelien die Fähigkeit, Bicarbonat zu resorbieren, sowie Ammoniak zu produzieren, eingebüsst haben, sodass Ca als Base vermehrt im Urin ausgeschieden wird. Es kann dann zum Bilde der *Nephrocalcinosis Lightwood—Albright* und zur *Nephrolithiasis* kommen.

2. Ferner ist der untere Nephronabschnitt aufsteigenden Infektionen viel eher ausgesetzt als der durch den Engpass der Henle'schen Schleifen und durch den Strom des noch sehr reichlichen glomerulären Filtrates geschützte proximale Abschnitt. Schon ALBRIGHT erwähnt nebenbei die Möglichkeit, dass aufsteigende Nierenerkrankungen wie etwa eine Pyelonephritis nur den distalen Tubulusabschnitt schädigen und dadurch eine *lower nephron nephrosis* erzeugen können.

3. Der distale Tubulus entbehrt des Schutzes durch die Kurzschlussfunktion des juxtamedullären Nebenkreislaufes (TRUETA).

Nach unseren Erfahrungen lassen sich die Symptome der langsam sich entwickelnden *lower nephron nephrosis* folgendermaßen ordnen:

I. Störung der Wasser-Rückresorption:

1. Grad: Überschießende H_2O -Ausscheidung beim Dilutionsversuch
2. Grad: Verzögerte H_2O -Ausscheidung (Nycturie)

3. Grad: Herabsetzung des Konzentrationsvermögens im Konzentrationsversuch bis zur Isosthenurie.

Störungen der Wasserrückresorption treten allerdings auch bei Insuffizienz des proximalen Tubulus in Erscheinung, denn Wasser wird (s. Abb. 2) im Bereich des ganzen Tubulus rückresorbiert. Es sei nur an die diabetische Polyurie erinnert: nicht nur bleibt hier die mit der Glukoserückresorption einhergehende Wasserresorption aus, sondern der hohe Glukosegehalt des Urins hält Wasser auch im distalen Tubulus zurück. Vielleicht beruht auch die schon frühzeitig auftretende Polyurie und Nycturie bei der chronischen Aminoacidurie wenigstens teilweise auf der mangelhaften Wasser-Rückresorption im proximalen Tubulus.

II. Störung der Einregulierung der Elektrolyte der extrazellulären Flüssigkeit Na und Cl (Ionolabilität, Hyper- und Hypoelektrolytämie), wobei Na und Cl nicht immer parallel schwanken.

III. Störung des Säurebasengleichgewichtes:

- a) Das pH des Urins rückt immer näher an dasjenige des Blutes heran.
- b) Hemmung der Ammoniakproduktion: Herabsetzung des Ammoniakkoeffizienten.

IV. Hypertension, wahrscheinlich infolge Reizung zur Mehrproduktion der Renin-erzeugenden Zellsprossen.

Dagegen fehlen bei der reinen Nephropathie des distalen Tubulus die glomerulären Symptome wie stärkere Albuminurie, Hämaturie, Retention harnfähiger Stoffe usw. Allerdings wird im Endzustand häufig auch das Glomerulum in Mitleidenschaft gezogen.

In der Regel treten die Symptome der lower nephron nephrosis in der erwähnten Reihenfolge auf; allerdings gibt es zahlreiche Ausnahmen, so kann sich die Hypertension lange vor der Störung der Einregulierung des Säurebasengleichgewichtes einstellen oder, wie dies bei der Nephronophthise der Fall ist, die Hypertension kann ganz ausbleiben, auch wenn die Erkrankung bereits auf das Glomerulum übergegriffen hat, wahrscheinlich weil bei der Nephronophthise als einer degenerativen Erkrankung der entzündliche Reiz auf die Renin-produzierenden Zellen in Wegfall kommt.

Eine Erkrankung des distalen Tubulus, auf die ich im Folgenden nicht eingehen werde, besteht darin, dass die Säurebasenregulation Schaden gelitten hat, sei es, weil das Bicarbonat-Ion HCO_3^- nicht rückresorbiert wird, sei es, dass die Nieren die Fähigkeit verloren haben, das „organische“ Kation NH_4^+ in genügender Menge zu produzieren. Folge davon ist die Abgabe in grosser Menge der anorganischen Basen Na^+ , K^+ , Ca^{++} usw. zur Neutralisation der Säureäquivalente. Es resultiert in der extrazellulären Flüssigkeit eine Chloracidosis und im eingedickten Urin in den Sammelröhrchen und im Nierenbecken der Ausfall von Calciumphosphaten und Carbonaten, was einerseits zur *Nephrocalcinosis* (LIGHTWOOD—ALBRIGHT) der Markpyramiden, anderseits zu Nierensteinen (Nephrolithiasis) führt.

Von den übrigen Formen der lower nephron nephrosis möchte ich heute nur 2 Krankheitsbilder, die wir in den letzten Jahren eingehend studieren konnten, hervorheben. Für das erste Krankheitsbild haben wir zusammen mit den Pathologen v. ALBERTINI und UEHLINGER und dem Genealogen HANHART 1951 den Namen *familiäre juvenile Nephronophthie* vorgeschlagen. Die ersten Beobachtungen reichen auf das Jahr 1926 zurück. In der einen Familie erkrankten sämtliche 5 Kinder, alles Knaben, im Alter von 2 Jahren; drei davon starben mit 6 Jahren an Urämie, zwei haben dieses kritische Alter noch nicht erreicht. In der zweiten Familie erkrankten 3 von 5 Kindern und zwar 2 Knaben und 1 Mädchen. Von den 8 von Nephronophthie befallenen Kindern waren also 7 Knaben und nur 1 Mädchen. Anamnese und Verlauf sind in allen Fällen auffallend ähnlich. Der Beginn ist schleichend, unmerklich; zuerst haben wir nur die Symptome der lower nephron nephrosis vor uns, nämlich 1. Polydipsie, Polyurie, Nycturie; 2. als Zeichen der gestörten Einregulierung der Elektrolyte häufig Hyperelektrolytämie; 3. die frühzeitige Störung der Aufrechterhaltung des Säurebasengleichgewichtes verrät sich in einem Sinken der Alkalireserve, im Unvermögen, einen sauren Urin zu produzieren und den Ammoniakoeffizienten zu erhöhen. Bis zuletzt fehlen sämtliche Zeichen einer Schädigung des Glomerulums im Sinne einer

erhöhten Durchlässigkeit, das heisst eine Albuminurie fehlt zuerst und ist auch im letzten Stadium nur geringfügig. Oedeme fehlen immer. Erst nach Jahren stellen sich Zeichen einer Erschwerung der Glomerulumpassage als RestN-, Phosphaterhöhung usw. ein. Der Blutdruck ist zuerst normal, später nur ganz wenig erhöht, weil infolge Fehlens arteriosklerotischer oder entzündlicher Veränderungen es weder zur Ischämie der Glomerula noch zu einer entzündlichen Reizung der Reninproduzierenden Sprossen kommt. Die Kinder sterben schliesslich unter dem Bilde der stillen Urämie.

Pathologisch-anatomisch findet man eine Hyalinose der Basalmembran der Tubuli, Atrophie und gelegentlich Erweiterung der Nierenkanälchen und eine hyaline Verödung der Glomerula, die ohne jeglichen Entzündungsvorgang, insbesondere ohne Halbmondbildung vor sich geht. Die Arteriolen zeigen keine sklerotischen Veränderungen. Das interstitielle Gewebe zwischen den untergehenden Nephronen ist gewuchert, stellenweise von Rundzelleninfiltraten durchsetzt. Man könnte demnach von einer chronischen interstitiellen Nephritis sprechen. Beide Pathologen, Prof. v. ALBERTINI und UEHLINGER, fassen die interstitiellen Lymphozyteninfiltrate als sekundäre resorptive Begleitprozesse auf und sehen die primäre Störung im Untergang des hochwertigen Nierenparenchyms. Die Diagnose interstitielle Nephritis stützt sich nur auf das anatomische Schlussbild, wird aber dem Entwicklungsgang des Nierenprozesses nicht gerecht. Wir haben daher auf diesen Namen bewusst verzichtet.

Weder in der Anamnese noch bei der pathologisch-anatomischen Untersuchung finden sich Zeichen einer Entzündung. Auch fehlen arteriosklerotische Veränderungen, sowie eine übergeordnete Stoffwechselstörung, die zu einer Schädigung des distalen Tubulusapparates hätte führen können. Wegen der Homochronie des ganzen Verlaufes glauben wir, dass es sich um einen erbbedingten vorzeitigen Aufbrauch des Nierenparenchyms, des Nephrons handelt, wobei der distale Tubulusabschnitt zuerst ergriffen wird. Daher der Name „*Nephronophthie*“. Wir vermuten, dass der gleiche Mechanismus des vorzeitigen Auf-

brauches des Nierenparenchyms des Nephrons nicht nur in den eben geschilderten familiären Fällen, sondern viel häufiger vorkommt. Wahrscheinlich liegt er auch mancher kryptogenetischen Schrumpfniere manchen „chronischen“ interstitiellen Nephritiden der Erwachsenen zugrunde.

Eine ganz andere Genese hat das Krankheitsbild, wofür wir den Namen „Benigne“ *pyelonephritische* bzw. *postpyelonephritische Hypertension* vorschlagen möchten. Wir vermuten, dass bei diesem gar nicht so seltenen Krankheitsbild die Hypertension die Folge eines entzündlichen Reizes der Renin-produzierenden Zellsprossen (s. Abb. 1) ist, und nicht durch eine viel schädlichere allgemeine Ischämie der Nieren zustandekommt. Ausgangspunkt der Aufstellung dieses neuen Krankheitsbegriffes ist ein Fall von renaler Hypertension im Gefolge einer chronischen Pyelonephritis, bei dem wir vor 19 Jahren eine ganz falsche Prognose stellten und der sich heute bester Gesundheit erfreut. Nachdem wir diesen besonders markanten Fall erlebt hatten, stiessen wir immer wieder auf ähnliche Krankheitsbilder:

Der Knabe erkrankt mit 10 1/2 Jahren an Anfällen von Kopfweh, Übelkeit und Erbrechen. Man denkt an Migräne. Bald fällt auch eine Polyurie ohne Urinbefund auf. Mit 11 Jahren konstatiert man eine Hypertension, schwankend zwischen 160 und 180 mm Hg systolisch und 130—140 diastolisch. Nunmehr finden sich im Urin vereinzelte Leucozyten und Colibakterien und ganz wenig Eiweiss. Man diagnostiziert eine chronische Pyelitis. Die nähere Untersuchung deckt eine Hypostenurie und eine verzögerte NaCl-Ausscheidung auf, dagegen gar keine Zeichen einer Glomerulumsuffizienz. Im Augenhintergrund ausgesprochene Neuroretinitis angiospastica. Die Pyelographie deckt beidseits kolbig aufgetriebene Calices als Zeichen eines Schwundes der Markpyramiden infolge der Pyelonephritis auf. Man entlässt den Patienten mit sehr schlechter Prognose. Der Knabe übersteht jedoch ein Jahr später eine schwere rheumatische Pankarditis. Die durch eine Aorteninsuffizienz bedingte Senkung des diastolischen Druckes hat wahrscheinlich recht günstig auf die pyelonephritische Hypertension gewirkt. In den folgenden Jahren entwickelt sich der Knabe zu einem hochaufgeschossenen kräftigen Jüngling, der heute ans Heiraten denkt und ein eigenes Geschäft eröffnet hat. Die Augenhintergrundveränderungen sind restlos verschwunden.

Von den 11 Fällen unserer Beobachtung, bei denen wir die Diagnose benigne pyelitische Hypertension stellten und bei denen allerdings nicht immer alle Symptome vorhanden sind, sei nur einer besonders hervorgehoben:

Das jetzt 19 jährige Mädchen macht im ersten Lebensjahr eine Pyelonephritis durch. Man denkt an Appendicitis wegen Druckempfindlichkeit der rechten Seite. Später stellt sich eine Enuresis, Nycturie und Hyposthenurie ein. Mit 8 Jahren konstatiert man eine Hypertension. Das Mädchen geht normal zur Schule. Eine ausgesprochene Akromikrie und eine kleine Sella turcica mit Sellabrücke lassen an ein diencephales hypophysäres Leiden denken. Man diagnostiziert einen atypischen Diabetes insipidus. Pitressin hat aber auf die Nycturie und Polyurie keinen Einfluss. Das Ionogramm zeichnet sich immer wieder durch eine Hypernatriämie bei Normochlorämie aus, der Anionenausfall wird durch eine hohe Alkalireserve ausgeglichen. Hochgradige Isosthenurie. Der Ammoniakkoeffizient ist auffallend niedrig. Im Urin nur Spuren Eiweiss und ab und zu einige Leukozyten. Die Pyelographie zeigt rechts kolbig aufgetriebene Calices; die Einbuchtung der Markpyramiden fehlt. Bei der Cystochromatoskopie wird rechts viel weniger blauer Urin als links ausgeschieden. Also die typischen Zeichen einer chronischen Pyelonephritis rechts.

Die Symptome der benignen pyelitischen Hypertension lassen sich folgendermassen zusammenfassen:

1. Das führende Symptom ist die Hypertension mit mehr oder weniger ausgesprochenem Fundus hypertonicus oculi.
2. Pyelonephritische Harnbefunde, die zeitweise ganz fehlen können.
3. Polyurie und Nycturie, die häufig eine Enuresis zur Folge haben.
4. Pathologischer Verdünnungs- und Konzentrationsversuch.
5. Störung im Elektrolytaufbau des Serums, Hyperelektrolytämie oder Hypochlorämie mit kompensatorischer Zunahme der Alkalireserve usw.
6. Pathologisches Pyelogramm mit einer kolbigen Auftreibung der Calices beider oder nur des einen Nierenbeckens.

Das eine oder andere dieser Symptome kann im konkreten Fall fehlen. Unerlässlich für die Diagnose sind die beiden Kardinalsymptome Hypertonie und chronische Pyelitis bzw. pye-

litische Anamnese. Verdacht auf das Vorliegen der benignen Hypertension muss eine Enuresis erwecken, die erst mehrere Jahre, nachdem das Kind bereits bettrein war, im Anschluss an ein Nierenleiden auftritt.

Schon lange ist es bekannt, dass chronische Nephropathien das *endokrine System* beeinflussen können. Ich brauche nur an die sekundäre Hyperparathyreose bei renaler Phosphatretention zu erinnern. Bei der Chronizität unserer Fälle von benigner Hypertension ist es daher nicht verwunderlich, dass sich hormonale Gegenregulationen als endokrine Störungen manifestieren können, die gelegentlich zu Fehldiagnosen Anlass geben. Wir haben einige solcher Symptome tabellarisch zusammengestellt. Eigenartig ist die Neigung zu Hochwuchs, was vielleicht mit der Hemmung der Ausreifung der sekundären Geschlechtsmerkmale zusammenhängt, waren diese doch in 2 Fällen mangelhaft entwickelt; in einem anderen Falle, der allerdings vielleicht etwas *sui generis* ist, waren sie umgekehrt eher verstärkt. Wahrscheinlich sind die endokrinen Störungen als Begleiterscheinungen kompensatorischer Vorgänge aufzufassen. Man könnte mit ALBRIGHT von Pseudoendokrinopathie sprechen, denn wie bei der Pseudohypoparathyreose liegt nicht primär eine endokrine Störung vor, sondern eine solche des Erfolgs- oder Endorgans, nämlich der Nieren.

Mit der Bezeichnung „benigne“ pyelische Hypertension haben wir uns, was die Prognose anbetrifft, festgelegt und zwar bei einem Krankheitsbild, dessen Hauptsymptom im allgemeinen zu einer sehr dubiosen Prognose berechtigt. Da wir unsere Patienten über Jahre, ja Jahrzehnte hinaus beobachten konnten und heute der Allgemeinzustand dieser Patienten durchaus befriedigend ist, auch wenn die Hypertension noch weiter anhält, sind wir doch wohl berechtigt, von benigner Hypertension zu sprechen und sie im Gegensatz zu der malignen, von einer Ischämie des Glomerulums herrührenden renalen Hypertension der chronischen Glomerulonephritis zu stellen. Ob diese benigne Hypertension auch nach 2—3 Jahrzehnten noch das Epitheton „benign“ verdienen wird, bleibe dahingestellt. Für den Kinderarzt genügt es zu wissen, dass davon befallene Kinder jahr-

Tabelle.

Auf einer endokrinen Dysfunktion beruhende Symptome bei der benignen pyelitischen Hypertension. „Pseudoendokrinopathien“.

Fall und Alter am 1.1. 51	Akro-makrie	Akro-mikrie	Hoch-wuchs	Poly-cytämie	Adi-positas	Sekundäre Geschlechts-merkmale
Fall 1 29 ⁷ / ₁₂ j.			+			vermindert
Fall 2 19 ¹ / ₁₂ j.		+				vermindert
Fall 3 14 ¹⁰ / ₁₂ j.			+	+		verstärkt
Fall 4 23 ⁶ / ₁₂ j.	+		+			normal
Fall 5 14 j.			+			normal
Fall 6 20 ¹ / ₁₂ j.					+	normal
Fall 7 20 ¹⁰ / ₁₂ j.			+	+		normal

zehntelang ohne einschränkende strenge diätetische und sonstige Vorschriften am Leben bleiben und sich normal entwickeln können.

Allerdings ist es im konkreten Fall nicht leicht, die maligne von der benignen Hypertension auseinanderzuhalten. Für den Arzt wird die Situation dann besonders heikel, wenn, wie in einigen unserer Fälle, nur die eine Niere pyelonephritisch erkrankt ist und die Frage auftaucht, ob man sie herausnehmen soll, um die Hypertension zu beheben. In einem unserer Fälle von einseitiger Schrumpfniere mit Hypertension gelang es, nach der Nephrektomie den Blutdruck in kurzer Zeit zu normalisieren und auch eine schwere „Myokardschädigung“ bereits nach 2 Wochen vollständig zum Verschwinden zu bringen. In einem andern Fall, wo auch zuerst glomeruläre Störungen fehlten, starb das Kind an einer Urämie. Bei der Autopsie fand man auch in der nicht geschrumpften Niere schwere Veränderungen

im Sinne einer Arteriosklerose. Hier war zweifellos die Hypertension malign. Es wird die Aufgabe der nächsten Jahre sein, Tests zu finden, die erlauben, die benigne von der malignen Hypertension, die nur von einer Niere ausgeht, auseinanderzuhalten.

Wir haben die Symptomatologie der lower nephron nephrosis keineswegs erschöpft. Hierher gehört auch das Crush-Syndrom beim Transfusionschock, nach Zertrümmerung grosser Muskelgebiete, bei überdosierter Sulfonamidarreichung, wobei die distalen Tubulusabschnitte mit Methaemoglobin, Myoglobulin, Sulfonamidkristallen usw. blockiert werden. Unter die chronischen Formen wäre noch die Nephrocalcinosis des distalen Nephrons (LIGHTWOOD—ALBRIGHT) sowie die Nierenschädigung bei der D-Hypervitaminose zu rechnen.

Ich wollte mit diesem Vortrag nur darauf hinweisen, wie die moderne Kenntnisse in der Physiologie und Pathologie uns die Möglichkeit gibt, etwas tiefer in das Wesen mancher Nephropathien einzudringen und dadurch auch prognostisch und therapeutisch besser zu handeln. Vieles an meinen Ausführungen ist hypothetisch und wird morgen überholt sein. Hypothesen helfen uns, neue Tatsachen aufzudecken und diese werden ihren Wert beibehalten.

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CASE REPORTS

Primary Hemangio-Endotheliosarcoma in the Liver of Children¹

by

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The rare occurrence of primary sarcomatous tumours in the liver, and the difficulties arising when the clinical diagnosis is to be made, justify the publication of this case.

A review of the existing literature showed some disagreement regarding both the classification and the correctness of the diagnosis in the cases described. The tumours are termed: angiomas, hemangiomas, endotheliomas, sarcomas, and various combinations thereof. Metastases from these tumours have been found in lungs, pancreas, bones, skin, and retroperitoneal gland, among others.

Etiology: HERXHEIMER (1930), for instance, holds that, since the primary sarcomas are most frequent in children, they are congenital and due to abnormal development of the connective

¹ Read before the Danish Pediatric Society, December 13, 1950.

tissue of the liver. In adults he believes that liver cirrhosis may be presarcomatous. MAC MAHON et al. (1947) have published a case of primary endotheliosarcoma in the liver of a man aged 70. A thorotrast injection was believed to be the cause of the formation of this tumour. Thorotrast had been injected in order to demonstrate, by X-ray, syphilitic gummata in the liver.

In cases with hemangio-endotheliomas in places other than the liver the question arises whether they are metastases or multiple congenital hemangiomas (SWEED and WEINBERG 1950). There is some disagreement on this point. However, the fact that the liver has a well-developed endothelial apparatus supports the theory of a primary occurrence in this place.

Concerning previously described cases reference may be made to the papers mentioned below, where the clinical picture is described in greater detail. These papers contain further supplementary references to literature.

KUNSTADTER (1932) has collected and described 15 cases, including his own, of hemangio-endotheliomas in the livers of children. BEREZIN et al. (1948) mention a further 6 cases. BEREZIN's own case occurred in a girl 9 days old, the youngest patient reported with the disease. In addition MUSSA (1947), SWEED and WEINBERG (1950), and WILLEFORD and STEMBRIDGE (1950) have reported one case each. The latter was, however, a case of liver sarcoma in a girl aged 6 years. VIDEBAEK (1946), who has described a case of hemangio-endothelioma (histologically benign) in a 2 1/2 months old infant, mentioned 33 previous cases. Of these, 14 were infants, the oldest 2 1/2 years and the youngest 1 month, average age 8 months. Only one more such case has been described in Danish literature, by LENDROP (1893). This was a case of liver sarcoma in a 4 months old infant.

Case History: Boy almost 12 months old. Admitted to the Surg. Dept. A, Københavns Amtssygehus, Gentofte, on Aug. 13th, 1950. Admitted with the diagnosis of "acute obstruction due to intussusception".

Mental and physical development normal. At the age of 8 months he had a mild attack of bronchitis, but had been otherwise healthy until 17 days before admission. Since then anorexia and

loose, yellowish stools, screaming spells, specially when touched on the stomach. For a short period his temperature rose to between 38 and 39° C, but it fell to normal again. During the 48 hours before admission the patient became increasingly restless and anemic.

Physical examination: On admission somewhat apathetic, whimpering, slightly restless, and anemic; not icteric. No dyspnea, but some uncharacteristic coughing. No peripheral adenitis except for a few small glands on the neck. State of nutrition good. Tongue moist. Slight reddening and swelling of the fauces with a few patches. Nothing abnormal in heart & lungs. Unmistakable tenderness in the abdomen below the right costal margin where there was also an indefinite resisting mass palpable. This mass was later recognized as an enlarged liver. It increased considerably in size during the next 48 hours, gradually extending as far as 2 or 3 cm below the umbilicus and over to below the left costal margin. It was firm and tense with a smooth surface. Spleen not palpable. No ascites.

The day after his admission he developed an about six-penny-sized hematoma over the right eye. Temperature on admission 37.8° C; rose gradually to over 38° C. Pulse rate between 120 and 140. Stools light and of normal consistency. No vomiting.

Investigations: Straight X-ray of the abdomen showed a large soft-tissue shadow below the right costal margin. No dilatation of intestines, nor fluid level. Ba enema normal. X-ray of thorax: massive opacity of the entire left field. In addition there were a few round condensed patches in the right field close to the hilus about the size of a penny. Slight displacement of the mediastinum towards the right.

Urine cloudy (urates), no albumen nor bile pigments. Hb: 46 % (Zeiss). Bleeding time considerably prolonged. White cell count 11 200 per cc. Slide from the peripheral blood and bone marrow puncture (SØEBORG OHLSEN) showed pronounced anisochromia and a few erythroblasts in the peripheral blood. Shift to the left in both the red and the white blood system. No evidence of leukemia.



Fig. 1. The liver invaded by the hemangio-endotheliosarcoma.

Therapy: Penicillin 100 000 units and aureomycin 100 mg, both six hourly. Blood transfusion intratibially 150 ml on two occasions. 1 mg vitamin K.

Course: After admission the boy's condition deteriorated quickly. He grew pale, increasingly dyspneic, and died after 48 hours.

Autopsy: Several small hemorrhages in the skin. The mucous membranes of pharynx, larynx, trachea, and bronchi slightly congested. In the left pleura 200 ml and in the right a small amount of blood-stained fluid. Irregularly outlined nodes pro-

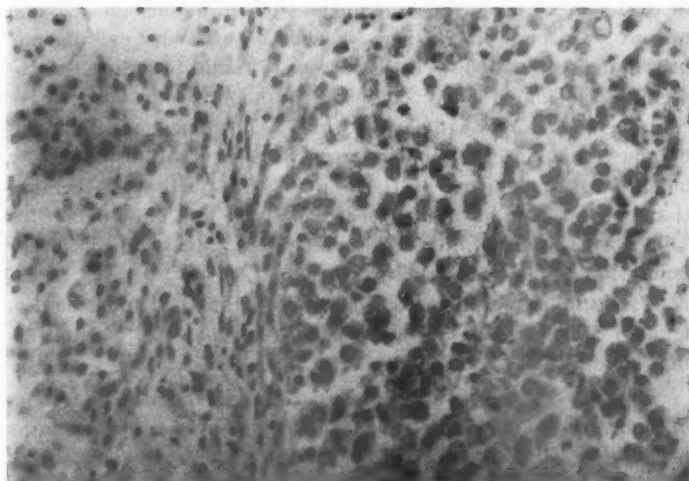


Fig. 2. Hemangio-endotheliosarcoma adjoining the compressed liver tissue.
× 100.

jected on the pleural surfaces as well as the cut surfaces of the lungs. They were from 2 to 5 cm in diameter. Along the borders the tissue was frayed by hemorrhage; centrally there was, in many, a yellowish-white firmer area. The adjacent lung tissue was somewhat edematous.

Liver large (weight 600 g). Surface coarsely nodulated but capsule smooth, however. A cut through the liver revealed several nodes, from 5 to 10 cm in diameter and with irregular outlines. (Fig. 1). Along the borders of these nodes the tissue was excessively blood-filled, angiomatous. More centrally many of them contained whitish firmer areas. Remaining liver tissue slightly reddish.

The remaining organs were normal.

Microscopy (SØEBORG OHLSEN) (Fig. 2): Sections of tumour tissue from the liver and of metastatic nodes from the lung tissue showed these to be constructed of endothelial, roundish or polygonal cells with a rather scant finely granular cytoplasm and round

or oval sharply outlined, large nuclei with large nucleoli. Several mitoses. In some places there seemed to be slender cytoplasmic off-shoots between the cells. Areas were found in which the tumour tissue had a fairly compact character, while other parts contained numerous capillaries, which seemed partially bounded by the tumour cells. Further, areas were seen to be split up by hemorrhage and edema. In the sections from the liver the tumour tissue was seen to have displaced liver tissue and bile ducts.

Sections from thymus, suprarenal gland, kidney, and pituitary body showed normal structures.

The tumour was derived from endothelium and must be designated as: *endotheliosarcoma, partially angiomatous*. Complicating edema and hemorrhage.

Diagnosis: The above case was one of angio-endotheliosarcoma in the liver with metastases to the lungs in a boy almost 12 months old.

Discussion. The course of illness was here, as in most other cases, very short, beginning with fatigue, anorexia, at times intense pain, below the right costal margin. These symptoms are very often accompanied by loose stools. A rapidly progressive anemia is also a common sign. Occasionally erythroblasts and immature myeloid cells have been found in the peripheral blood, as signs of extramedullary hematopoiesis. In some cases jaundice and ascites have been present. The most characteristic sign is, however, the enlarged liver, and specially the enormous and rapid growth of the latter. In several cases it has been possible, as in the present case, to follow its growth from day to day. This is due to hemorrhage into the tumour tissue. A contributory cause of the considerable hemorrhage may possibly be the prolonged bleeding time, which is probably the result of the obstructed liver function. Such a prolonged bleeding time has not previously been mentioned, however.

The prognosis is bad, as all patients have so far died of the disease. It is doubtful if any form of treatment is efficient even if the diagnosis is made, either by abdominal exploration or by the aid of an aspiration trepan.

Summary

A brief review is given of the etiology and of previously reported cases of primary endotheliosarcomas of the liver. A case is described of hemangio-endotheliosarcoma in a boy almost 12 months old, who died after 3 weeks of illness. Autopsy performed. A brief account of the course of illness is given.

O. STEINICKE NIELSEN: *Hémo-angio-endothéliosarcôme primaire du foie de l'enfant.*

Une brève critique nous parvient sur l'étiologie et la publication antérieure de cas d'endothéliosarcôme primaire du foie. Un cas d'hémo-angio-endothéliosarcôme est décrit chez un garçon de 12 mois à peine, mort après 3 semaines de maladie. L'autopsie est effectuée. Suit un bref compte-rendu du cours de la maladie.

O. STEINICKE NIELSEN: *Primäres Hämangio-Endotheliosarkom in der Leber von Kindern.*

Der Verfasser gibt eine kurze Übersicht über die Ätiologie und früher mitgeteilte Fälle von primären Endotheliosarkomen in der Leber. Er beschreibt einen Fall von Hämangio-Endotheliosarkom bei einem knapp 12 Monate alten Knaben, der nach dreiwöchiger Krankheit starb. Autopsie wurde vorgenommen. Kurzer Bericht über den Verlauf der Krankheit.

O. STEINICKE NIELSEN: *Hemangio-endotheliosarcoma hepatico primario en los niños.*

Se hace una breve revision sobre la etiología y sobre los casos existentes en la literatura de endoteliosarcomas primarios de hígado. Se comunica un caso de hemangio-endoteliosarcoma en un niño de unos 12 meses, muerto a las 3 semanas de enfermedad. Se pudo practicar autopsia. Coméntase de un modo sucinto el curso de la enfermedad.

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The de Toni—Fanconi Syndrome with Cystinosis¹

by

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Renal rickets and renal inhibition of growth have long been recognized in clinical medicine. Accounts of this condition have been given in the Scandinavian countries by SUNDAL (1932), SALVESEN (1934), SVENSGÅRD (1934), BUCH (1939), TOMENIUS (1944), STORSTEIN (1945) and by TUDVAD (1948) among others. KAJSER has published in this journal a summary of the many publications on this subject up to 1940.

In 1933, FANCONI distinguished the hypophosphatemic form of renal rickets from the hyperphosphatemic form. On the basis of three cases of his own and two cases from the literature (DE TONI 1933, DEBRÉ et al. 1934) he described a new and clearly defined clinical picture which differed first and foremost from that of the hyperphosphatemic form of renal rickets by its early onset, by marked inhibition of growth, and by characteristic changes in the urine and blood. In the urine glucose was demonstrable in addition to albumin, and there was a marked increase of the excretion of the organic acids and ammonia. The most important changes in the blood depended on marked hypophosphatemia with practically normal calcium and phosphatase figures and on the early onset of acidosis. During the following years several reports have come from various European countries and America about this condition which is best known as the de Toni—Fanconi syndrome.

¹ A preliminary report of this case was given to the Danish Pediatric Society, January 17th, 1951.

As early as 1924, the pathologist LIGNAC had drawn attention to a condition characterized chiefly by disease of the kidneys, inhibition of growth, rickets and disturbances of cystine metabolism. The existence of the latter was confirmed by the post-mortem demonstration of deposits of cystine in various organs, the spleen in particular. In 1937, FANCONI succeeded in demonstrating cystine in the urine of one of his patients, and in 1940, LOOSER (1944) found large deposits of cystine in several organs of one of Fanconi's patients examined post-mortem.

Since then several studies have appeared, coming chiefly from Switzerland and Holland and showing how close is the connection between the de Toni—Fanconi syndrome and cystine disease. Several investigators have thus identified the one with the other. But certain observations during the last few years show that they are not always identical. Deposits of cystine have not been demonstrable in every case of the de Toni—Fanconi syndrome coming to necropsy. In a study published in 1949, FANCONI and BICKEL gave an account of a typical case of this syndrome in which cystinosis was not found, whereas, on the other hand, there was glycogenosis of the von Gierkes type.

In 1949, FREUDENBERG published a survey of 16 cases of cystinosis, which had hitherto been reported on and definitely verified (the term cystinosis being given to cases of cystine disease with deposits of cystine in the organism). In American quarters it is held that cystine disease (including the asymptomatic cases of cystinuria) is probably the most common of the anomalies of metabolism belonging to the group of "inborn errors of metabolism." The disease can therefore hardly be considered as a rarity, although it is certainly not common.

Little seems to be known in the Scandinavian countries about both the de Toni—Fanconi syndrome and cystinosis. In 1941, PLUM demonstrated a case of the de Toni—Fanconi syndrome at a meeting of the Danish Pediatric Society. In 1949, in Sweden, D'AVIGNON and VAHLQUIST described a case of cystinosis. As far as I can ascertain, no other cases of this disease have hitherto been published in the Scandinavian countries. A description will therefore be given of a case in which this disease was diagnosed in the autumn of 1950 at the Children's Hospital, Martinsvej, Copenhagen.

Case report. A baby girl, born on December 10th, 1948, was admitted to hospital on August 25th, 1950, remaining there till October 14th of the same year. From then she was under close observation until she was readmitted to hospital on December 13th, 1950. She remained in hospital till December 21th, 1950, and died on December 28th of the same year.

The parents, not related to one another, were healthy. The mother was the second of two children, and her parents and sister were healthy.

The father was the second of three children, all of whom, as well as his parents were healthy. There was no record in the families of the parents of any death early in childhood. There was no family history of dwarfism, rickets, nephrolithiasis or other disease of the kidneys. The patient was an only child and was born at term after normal and uncomplicated pregnancy followed by a natural confinement. Weight at birth 3,100 g, length 50 cm. Breast-fed for the first month. Artificial feeding subsequently. When about 1 month old, she was started on cod liver oil and this was continued until she was 5 months old. Later on she was again given cod liver oil, one teaspoonful daily from October 1949 to April 1950. Thereafter a concentrated cod liver oil preparation, containing about 800 vitamin D units, was given daily till her admission to hospital in August, 1950. From the age of 5 months she was given potatoes, fruit and vegetables, but no ascorbic acid preparations. Her development was normal during the first year, though her mother said she never ate well. She could walk by herself when 12 months old. Throughout her first year she was subject to infections (chiefly colds), but was in other respects healthy till she contracted measles when 16 months old.

Since then her appetite has dwindled more and more, and she began to refuse food during the few months before admission to hospital. On the other hand she was always thirsty, drinking a lot and passing much urine. During the last few months the action of her bowels had been irregular, the motions hard and nodular. No vomiting. Streaks of blood were present in the motions on August 23rd, 1950, and she was admitted to a surgical hospital for observation, intussusception being suspected. This was not confirmed, but as she was listless and her appetite was remarkably poor, she was transferred to the Children's Hospital.

In hospital (for the first time) between August 25th and October 14th, 1950.

She was pale and listless on admission, the state of general nutrition a little below par. Weight 9,380 g, length 78 cm. (The normal length for her age being 85 cm.) The anterior fontanelle was open, measuring about 1 1/2 by 1 1/2 cm. Definite craniotabes and Harrison's sulcus. Epiphysial swelling of the wrists and, to a lesser degree, of the ankles. Legs slightly bowed, muscles relaxed and poorly developed. Teeth normal, no gingivitis. No abnormality found in the throat, neck, heart or lungs. Abdomen soft and of normal appearance, without any palpable distension. Liver and spleen not palpable. Reflexes normal. The urine contained protein and sugar. A leucocyte or two could be seen in each field, but the urine was otherwise normal.

Throughout her stay in hospital the patient whimpered and was irritable, suffering from anorexia, great thirst and obstinate constipation with lumpy stools. The weight curve swung slightly and tended to fall, around 9,380 to 9,000 g. The temperature was normal to sub-normal all the time without great oscillations. The blood-pressure normal. Diuresis was considerable but difficult to measure as she suffered from constant incontinence. The urine was usually light, clear or slightly cloudy, and always definitely acid, with a pH under 6. Specific gravity 1012 on the average, but varying from 1001 to 1020. Small quantities of protein (Esbach $< 1/4\%$) always present in the urine which gave a positive Fehling reaction, weak or moderate (sugar always less than 1%) Tests for acetone and aceto-acetic acid negative all the time. Under the microscope few formed elements, erythrocytes not more than 0-2 per field, leukocytes not more than 3-5. On a couple of occasions a few hyaline casts, and on one occasion numerous granular casts were seen. An urographic examination after an intravenous injection of 15 ml of diodone showed quite a weak contrast excretion on both sides. The shadows cast with the kidneys seemed to be normal, and there was no sign of obstruction or malformations. A cystoscopic examination showed the lining of the bladder and openings of the ureters to be normal. Catheterization of the ureters proved easy on both sides. A radiological examination with direct pyelography showed a normal pyelogram and normal shadows cast by the ureters and bladder. Clearance tests: Urea clearance (two tests) 90% and 77%. Potassium clearance 3.7 and 3.2. Inulin clearance 32.1 and 51.0. No demonstrable sodium in the urine.

The blood: The hemoglobin varied between 86% and 95% (Haldane). The sedimentation rate was about 20 mm. The antistreptolysin titre was 36 (normal). Wassermann negative. Blood urea 34 mg% September 4th, 26.7 mg September 14th. and 40.9 October 10th. Fasting blood sugar 76, 85 and 90 mg%. A glucose tolerance test (18 g as a 10% solution) gave a normal blood sugar curve without any signs of discomfort during the test. Bicarbonate 20.1 m. mol on September 4th, 24.4 m.mol on September 14th, and 19.9 m.mol on October 10th. Calcium on two different tests 11.6 and 11.1 m%. Phosphorus 2.7 mg% and 2.7 mg%. Phosphatase 11.7 and 10.1 Buch-units (normal), potassium 13.9 and 11.5 mg%. Sodium 300 and 286 mg%

A radiological examination of the bones showed the number of ossification centres within normal limits. The forearms, legs and thighs showed a beaker-shaped increase of width of the distal ends of the metaphyses whose bony structure was indicative of rickets. The head showed no radiologically demonstrable abnormalities.

The evidence being very suggestive of renal rickets of the de Toni-Fanconi type, further investigations were undertaken with cystinosis



Fig. 1 shows the patient (to the left) with a child of the same age (October 1950).

in mind. Crystals of cystine could not be found in the urine even after it had been rendered acid and kept standing for a long time. Neither cystine nor cysteine could be found by Sullivan's method at the Medical Laboratory in Copenhagen on October 2nd. On two subsequent occasions (as an outpatient), samples of urine gave a definite positive cystine reaction to Meyer's sodium-cyanid-nitroprussid method. The reaction was doubtful to the lead acetate test. The urine was examined on November 8th at the central laboratory of the Sahlgren Hospital, Gothenburg, where crystals of cystine could not be found. The lead acetate test and Sullivan's test for cystine (after the precipitation of protein) were negative. Paper chromatography showed a marked increase in the amino acids, tyrosin, phenylalanin, alanin, leucin and valin being found, but not any cystine with certainty. At the same laboratory and time, tests were made for serum-citric acid and phosphatase, serum colour, thymol turbidity, and the serum was examined by chromatography. There was a slight increase of the citric acid and phosphatase figures, whereas the icterus index (Meulengracht's figures) was 3 and

THE DE TONI—FANCONI SYNDROME

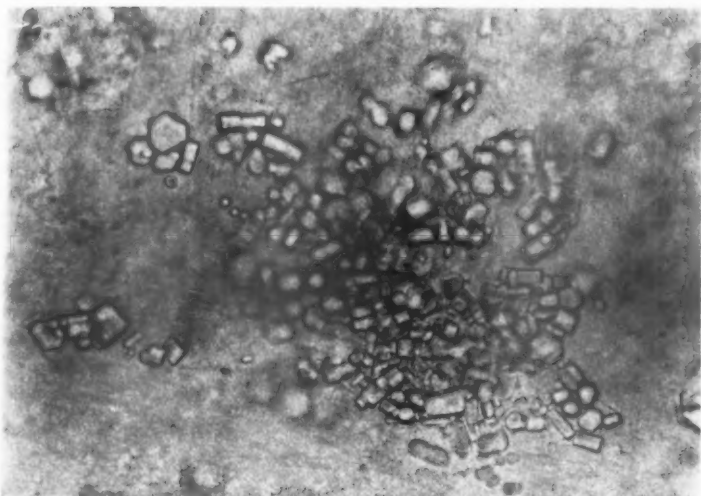


Fig. 2. Biopsy of the conjunctiva. An unstained, moist preparation showing masses of rectangular and hexagonal crystals.

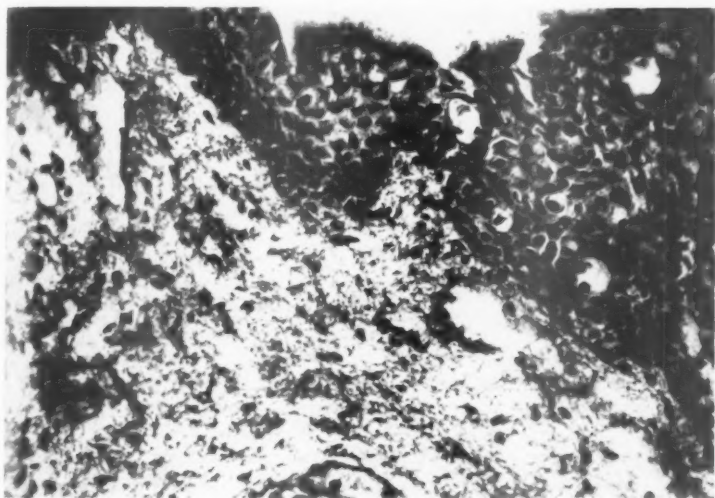


Fig. 3. Biopsy of the conjunctiva. Subepithelial, minutely partitioned, loose connective tissue which has presumably contained crystals.



Fig. 4. Biopsy of the conjunctiva. An oil immersion enlargement of crystals in the deeper layers of the connective tissue of the conjunctiva.

the thymol test 0.09 (the normal being 0.01 to 0.10). Conclusion: No definitely demonstrable damage to the parenchyma of the liver. Chromatography showed no increased figures for the amino acids in the serum in comparison with normal figures.

Bone-marrow puncture (the tibia) did not yield marrow perfectly suitable for examination. It contained much fat and very few cells in which crystals of cystine could not be found.

On October 10th, an examination of the eyes at the Eye Department of the Rigshospital (P. Brændstrup) yielded the following findings: "Vision seems to be perfectly normal, and there is nothing noteworthy about the size, position or movements of the eyes. On ordinary superficial inspection the cornea appears to be normal, and it shows no opacity on ophthalmoscopic examination. But on a slit lamp examination, the cornea is seen everywhere, particularly in the limbal areas, to be densely studded with small elements reflecting light. They are found to consist of crystalline deposits transmitting light. The shape of these crystals could not be determined."

Biopsy of the conjunctiva was then undertaken (P. Brændstrup), and the material thus obtained was examined by Harald Gormsen with the following results: "Haematoxylin-eosin-stained preparations were made without differentiation in hydrochloric acid-alcohol. Under the microscope no changes, particularly no crystal-like elements, could be seen in the epithelium of the cornea. At many points the connective tissue under the epithelium showed areas poor in cells, of a quite loose, finely-partitioned structure. Delicate fibrils formed the boundaries of small spaces which at many points were so regular in outline that they could very well have contained crystals. Diagnosis: Tissue changes which are presumably a manifestation of cystinosis."

When the patient was discharged from hospital on October 14th, 1950, her condition was much the same as it had been on admission. On discharge she was put on an all-round diet with a relatively high fluid content and an ample supplement of vitamins including 1600 vitamin D units daily.

In hospital (for the second time) between December 13th and December 21st, 1950.

She was readmitted for examination and further investigations. On the whole, she had thrived well since her last stay in hospital, having been fairly lively and happy, playing like a normal child without getting remarkably tired. But her appetite was still bad, particularly with reference to milk products. She was still constantly thirsty and constipated as before. On examination she was found to be rather pale and puny, her state of nutrition a trifle below the average. General

condition unaffected. Her muscles seemed to be firmer and with a better tone than when she was last in hospital. Length 78 cm as before (normal length for her age 87 cm), weight 9,650 g. Her head showed a slight hint of caput quadratum. The anterior fontanelle still open, about 1 1/2 by 1 cm, with firm margins. No craniotables now. Harrison's sulcus quite definite. Slight distension of the distal metaphyses of the forearms. No other pathological changes. Urine: Diuresis plentiful, approximately 800—1300 g. The urine light-coloured, slightly clouded and constantly acid. The pH, determined on two occasions with a potentiometer, was 5.41 and 5.80. There were always weak but definite positive albumin and sugar reactions. Quantitative tests for ammonia (formol titration) of three samples of day urine gave the following figures: 0.30 g in 580, 0.33 g in 600, and 0.31 g in 550 ml. It should be noted that these quantities did not represent the whole of the day urine as some of it was passed involuntarily. (The normal figures for NH_3 -excretion in urine 0.3—1.2 g in the 24 hours.) The report on the microscopic examination of the urine tallied with that on the patient's previous stay in hospital. The blood: Hemoglobin 92 %. Urea on December 14th, 38.8, and on December 20th, 58.6 mg%. Bicarbonate on December 14th, 23.6 m. mol, on December 19th, 17.0, and on December 20th, 20.5. Potassium 10.4 mg%. Sodium 331 mg%. Chloride 339 and 313 mg%. Calcium 11.8 mg%, phosphorus 2.9 mg%, phosphatase 13.3 Buch units. Cholesterol 258 mg%. Serum ascorbic acid 0.29 mg%.

A radiological examination of the upper and lower limbs now showed a quite slight beaker-shaped swelling of the ends of the bones and nothing else abnormal. Slit lamp microscopy again showed crystals in the cornea and the conjunctiva, a renewed biopsy of which showed on direct examination of the preparations masses of rectangular and hexagonal crystals presenting the features characteristic of cystine, being insoluble in alcohol, soluble in ammonia and giving a positive Wollaston reaction (on the addition of concentrated HCl to the preparation when the crystals turn into large bundles of needles).

Throughout her stay in hospital the patient seemed rather listless, and there was no change in her anorexia, thirst and constipation. She vomited now and then the day before she left hospital. On her discharge on December 21st, she was lively and good-tempered with general condition absolutely unaffected.

She lived only a week after discharge. During this week, which she spent at home, she was listless and unwell, vomiting several times and eating very little. There were no catarrhal manifestations, no fever nor diarrhoea. She was not so exhausted as to alarm her parents, and in particular there was nothing remarkable about her on the evening of December 27th. But next morning she was found to be mori-

Table 1.

This table gives the most important findings of the analyses of the blood during the two occasions on which the patient was in hospital.

	$\frac{4}{9}$ 51	$\frac{14}{9}$ 51	$\frac{10}{10}$ 51	$\frac{14}{12}$ 51	$\frac{10}{12}$ 51	$\frac{20}{12}$ 51
Urea mg%	34.0	26.7	40.9	38.8		58.6
Bicarbonate m. mol	20.1	24.4	19.9	23.6	17.0	20.5
Calcium mg%	11.6	11.4		11.8		
Phosphorus mg%	2.7	2.7		2.9		
Alkaline phosphatase (Buch- units)	11.3	10.1		13.3		
Sodium mg%	300		286	331		
Potassium mg%	13.9		11.5	10.4		
Chloride mg%				339		313

bund in bed. She was at once taken to hospital, but was dead when she came there.

Post-mortem examination: This was undertaken by Dr. Carl Jakobsen of the Copenhagen City Hospital who has kindly given his permission for the publication of the following brief, preliminary report: No immediate cause of death was demonstrable. On a macroscopic examination there was nothing unusual to note with regard to the organs apart from moderate changes in spleen and liver (see below). Crystals of cystine were histologically demonstrable in the following organs:

The spleen: It was not enlarged and was rather firm. On section it presented a uniform, greyish-red surface with numerous small and yellow spots standing close together and rather like dust. Numerous rectangular and hexagonal crystals could be seen in direct, moist preparations. Under the microscope enormous deposits of the same, characteristic crystals could be seen in the pulp, most often in the trabeculae and sometimes in a cape-shaped arrangement around the vessels. In other respects the structure of the spleen was normal, and there were no necrobiotic foci.

The liver: It was not enlarged, and its consistency was normal. On section and on closer scrutiny, the same dusty appearance as that noted in the spleen was seen, but was not so definite. Under the microscope numerous deposits, usually in small heaps, were seen, but they were smaller than those in the spleen. The structure of the liver was in other respects normal.

The lymphatic nodules: There was no enlargement of the lymphatic glands. A section of a para-aortic gland showed numerous heaps

of crystals in both cortex and medulla (outside the follicles). Normal structure without necrobiotic foci.

The bone marrow: Here there were numerous crystals which in some places were plainly intracellular.

The tonsils och thymus: Deposits were found in comparatively great numbers here also, but not in such profusion as in the above-mentioned organs.

The choroid plexus: numerous deposits.

The kidneys: These measured 8 by 4 by 2.5 cm, and 7 by 4 by 2.5 cm. The capsules could be easily detached and the surfaces of the kidneys were smooth, pale yellow, without areas of retraction. The surface on section a little firmer than usual, the cortex a pale yellow, the medulla rather dark, greyish-red with a hint of cyanosis. Histological examination showed small deposits of crystals in the interstitial tissues. In other respects the appearance of the kidneys did not differ from the normal in childhood.

The suprarenals: A few deposits were found in the medulla.

The stomach: The tunica propria of the mucosa showed a few deposits.

The lungs, heart, brain with pituitary body, meninges, tongue, uterus, ovaries, thyroid and parathyroid glands and pancreas: All these organs appeared to be perfectly normal, without any demonstrable deposits of crystals in them. The pelves of the kidneys, the ureters and bladder were perfectly normal, without any calculi.

In order to make sure that the above-mentioned crystals really consisted of cystine, samples of the spleen and liver were sent for chemical examination to the Medico-Legal Institute of the University at Copenhagen (Dr Phil. Frank Lundquist). The following is an extract of the report: "A quantitative analysis of free cystine was undertaken of the specimens of the organs concerned, use being made of a new method which is said to be strictly specific for cystine (NAKAMURA & BINKLEY; J. Biol. Chem. 173: 407, 1948). In the spleen 270 mg cystine per 100 g of tissue, and in the liver 160 mg per 100 g of tissue were found. A control test was made of the spleen of a man aged about 50 years: No reaction, i.e., less than 5 mg of cystine per 100 g of tissue. It should be noted that the content of dry substance in the alcohol-treated material (spleen 23 %, liver 27 %) does not differ to any important extent from that of the healthy tissue. In further attempts at identification, an effort was made to produce crystalline cystine from an extract of the spleen. After precipitation with trichlor-acetic acid (about 15 %) and filtration, the clear solution (corresponding to about 1 g of tissue) was evaporated down to 8 ml. The pH with acetate was about 4. In the course of a couple of hours, cystine crystallized out on standing at a temperature of 0° C. The hexagonal crystals were characteristic

of cystine in every respect (appearance, melting point and qualitative reactions)."

Comment: This 2-year-girl had suffered since she was 16 months old from anorexia, polydipsia, polyuria, constipation and inhibition of growth. On admission to hospital she presented a moderate degree of rickets, delayed growth in length, albuminuria, glycosuria, amino-aciduria and, possibly, cystinuria (a positive reaction to the sodium-cyanid-nitroprussid test.) She also presented hypophosphatemia with approximately normal calcium and phosphatase figures. The serum sodium figures were at the lower limit of the normal, the serum potassium figures were considerably below normal and the serum chlorine was reduced. The bicarbonate figures were usually a bit low, but there was no definite acidosis. Renal function seemed to be comparatively good: Specific gravity up to 1020, normal urea clearance, but a slight rise of the serum urea. The diagnosis of cystinosis depended on slit lamp microscopy of the cornea and biopsy of the conjunctiva. The diagnosis was subsequently confirmed by a post-mortem examination at which the presence of cystine in the organs was demonstrated chemically and by the characteristic histological changes.

This case presents certain features which are not in conformity, or only partially so, with the findings of earlier records of such cases. These features are in brief as follows:

1. The disease was apparently not hereditary (the urine of the parents also was examined for cystine with negative results).
2. There was a rapid and successful reaction to vitamin D treatment with moderate doses.
3. The urine was acid all the time, with low NH_3 -content.
4. There was no acidosis or at any rate only slight acidosis.
5. The serumpotassium figures were steadily falling and much below normal.

It is also remarkable that the kidneys presented a normal histological picture (apart from a few crystals in the interstitial tissues). Yet the disease had given rise to clinical manifestations for at least eight months.

No explanation is forthcoming of the cause of the patient's sudden death which was not preceded by any very alarming symptoms. It is tempting to regard this as an "electrolytic death" which may perhaps primarily be connected with her low serum-potassium.

Summary

A case of the de Toni—Fanconi syndrome is described in which the diagnosis depended on a slit lamp examination of the eyes and a biopsy of the conjunctiva. Lastly, attention is drawn to certain features which distinguish this case from the cases recorded earlier.

A. DRABLØS: *Le de Toni—Fanconi Syndrome avec Cystinose.*

On fait d'abord une revue générale du syndrome de de Toni—Fanconi avec cystinose. Fait suite alors le compte rendu d'un cas dans lequel le diagnostic dépendait d'un examen des yeux, par lampe à fente et d'une biopsie de la conjonctive. Enfin l'attention est attirée sur certains faits qui distinguent quelque peu ce cas de ceux rapportés précédemment.

A. DRABLØS: *Das de Toni—Fanconische Syndrom mit Zystinose.*

Der Verfasser gibt einen Überblick über das de Toni—Fanconische Syndrom mit Zystinose. Hierauf berichtet er über einen Fall, dessen Diagnose sich auf die Untersuchung der Augen mit der Spaltlampe und auf Biopsie der Bindehaut gründete. Schliesslich lenkt er die Aufmerksamkeit auf gewisse Züge, welche diesen Fall etwas von den früher registrierten Fällen unterscheiden.

A. DRABLØS: *El síndrome de de Toni—Fanconi con cistinosis.*

Se hace una revisión del síndrome de de Toni—Fanconi con cistinosis, relatándose al propio tiempo un caso en el cual el diagnóstico fué hecho con el examen ocular por la lámpara de hendidura y una biopsia de la conjuntiva. Se llama la atención sobre ciertos aspectos que caracterizan este caso diferenciándolo de otros descritos anteriormente.

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Craniostenosis and Vitamin D Resistant Rickets

by

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The term craniostenosis covers those deformities of the cranium which are due to premature ossification of its sutures (1), the shape varying with the site in such conditions as oxycephaly, scaphocephaly, etc. The literature contains several reports of craniostenosis associated with malformations and various other diseases of the skeletal system, particularly of the fingers and toes. Thus, oxycephaly has been de-

scribed in association with chondrodystrophy and osteogenesis imperfecta (2), and with Albers Schönberg's disease (3). Scaphocephaly has also been described in association with Albers Schönberg's disease (4).

The following case presents craniostenosis and Vitamin D resistant rickets—a combination which apparently has not been previously described. It is well known that Vitamin D resistant rickets is characterized by changes closely resembling the ordinary rickets of infancy, but these changes are not influenced by Vitamin D until large doses have been given (5).

Case History:

E. S., an only child, was born by Caesarian section on June 11th, 1946, after a normal pregnancy. Weight at birth was 4750 grams. The child was breast fed for one month, after which two-third milk was given until he was 8 months old. At this time he was given whole milk with an ordinary mixed diet. Two teaspoonsful of cod liver oil were given daily from the age of 2 weeks until 1 year, when intervals of several days would elapse between doses. Because he became a feeding problem in other respects, his mother began to give him plenty of milk—without measuring it. However, at about 1 year of age, it was noticed that he became increasingly bow-legged, and that his forehead was prominent. In other respects, he seemed healthy, and had no complaints. His condition was diagnosed as rickets, and treated for two months at Rogaland Hospital (August to October, 1947).

On admission to the hospital, a radiologic examination of both wrists and legs below the knees showed typical rickets. He was immediately given 5 ml of cod liver oil once a day, and this was increased after a short time, to 5 ml three times a day. After 1 month he was given 10 ml, three times, and this dosage was continued after his discharge. At discharge he was also given 250,000 international units of Afi D₂ forte, intramuscularly, as there was no sign of improvement in the rachitic condition. Two and a half months after discharge he was given an additional 500,000 units Afi D₂ forte, intramuscularly.

On February 3rd, 1948, a radiologic examination showed no improvement and he was readmitted to the Rikshospital on April 16th, 1948. His appearance on admission was healthy and his state of nutrition was about average. His weight was 11.5 kg (1.5 kg below normal); height 85 cm (3 cm below normal). It was noted that his head was long and narrow, with steep lines on both sides and prominent tubera frontalia. From the point where the frontal and parietal bones met, a ridge could be seen passing backwards in the midline, gradually disappearing. The fontanelles were not palpable, and there was no craniotabes. Circumference of the head was 49 cm (average at his age 47.93). A "rickety rosary" and Harrison's groove were present. There was enlargement of the ends of the bones at the wrists, knees and ank-

CRANIOSTENOSIS AND VITAMIN D RESISTANT RICKETS



Fig. 1 A. Roentgenogram of the left arm 19.4.48 showing rachitic changes particularly at the distal end of radius and ulna.



Fig. 1 B. Roentgenogram of the right wrist 17.9.49 showing considerable improvement of the rachitic changes.

CRANIOSTENOSIS AND VITAMIN D RESISTANT RICKETS

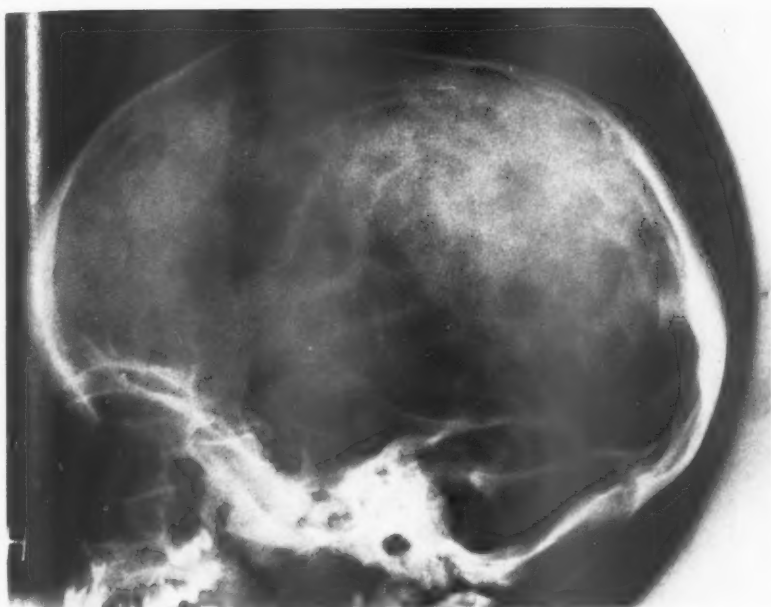


Fig. 2 A. Roentgenogram of the skull of the patient E. S. 19.4.48 sagittal projection showing premature closure of the sutures, increased impressions, and a prominence corresponding to the region of the large fontanelle.



Fig. 2 B. Roentgenogram of the skull of the mother 23.11.48 sagittal projection showing increased impressions in the posterior half, remarkably small lambdoid sutures and a hint of platybasia.

les, and the patient was markedly bow-legged (Fig. 3 A). Blood pressure was 100/80. Liver was palpable below the right costal arch. Spleen was not palpable. Brisk patellar and Achilles reflexes were present. The fundus oculi on both sides showed ill-defined optic disc margins, about 2 diopters prominence, suggesting that optic disc congestion was present on both sides. A neurologic examination showed no further abnormality, and the patient's intelligence seemed normal.

Radiologic examination of the limbs showed the long bones to be short and stumpy—the humerus in particular. The humerus and ulna on both sides showed slight arching, with a convexity to one side. Definite arching of the legs, above and below the knees, was present. In the areas corresponding to the growth zone, excavation was present, with cupping of the epiphyseal lamina as well as spreading and fraying. These changes were most clearly visible in the ankles and wrists (Fig. 1 A). There was normal development of the ossific centers. The vertebral column showed slight diminution of the thoracic kyphosis, and some diminution of the normal lordosis. There was nothing unusual about the shape of the pelvis. The skull (Fig. 2 A) showed increased impressions and a prominence in the sagittal plane, corresponding to the region of the large fontanelles, similar to a Crouzon's type of craniostenosis. The coronary suture was hardly visible and other sutures were very small. The thorax showed definite "rickety rosary," with enlargement of the peripheral portions of the ribs. On April 21st, 1948, he was given 500,000 units Afi D₂ forte, intramuscularly.

In view of the changes in the fundus oculi, which raised a suspicion of increased intracranial pressure, he was transferred (May 13th) to the Neurologic Department where he remained four months.

An examination of the fundus oculi shortly after admission showed the margins of the optic disc to be completely visible on the right side. They were plainly outlined on both sides, nasal and lateral, but were veiled and rather pale above and below. The limits were undefined on the left side; were pale grey with a prominence of 1 to 2 diopters. The impression was that the optic disc congestion was receding, with a question of incipient atrophy of the optic nerve.

Decompressive craniotomy was performed by Doctors ROVIG and TORKILDSEN, in four stages, with intervening intervals of several weeks between each stage. Two thin strips of cranium were cut out on the right—one of them in front near the coronary suture, the other near the transverse sinus. The same operation was made on the left side. The frontal "sutures" on the left side were linked up with the aid of a 2–3 cm furrow in the sagittal plane to the left of the sinus. The two "sutures" on the right side were prolonged to the left side to meet the earlier "sutures" on this side. Examination of the fundus oculi after



Fig. 3 A. Photo of the patient
E. S. 23.11. 48.



Fig. 3 B. Photo of the mother
23.11. 48.

the first two operations showed regression of the optic disc congestion, and this disappeared after the third operation.

On September 13th, 1948, he was readmitted to the Children's Department, remaining there until November 23rd, 1948. The right eyelid now showed slight ptosis. Brisk patellar and Achilles reflexes were noted, but no other significant neurologic findings were present. An ophthalmoscopic examination showed the optic discs to be normal.

A radiologic examination of the wrists on September 18th, 1948, failed to show any definite improvement in the rachitic condition, and from September 27th, 1948, he was given 12 drops (140,000 units) of Afi D₂ forte daily, orally. Two weeks later, a radiologic examination indicated improvement. From November 9th he was given 250,000 units of Afi D₂ forte daily, orally, and continued improvement was noted. Because of a misunderstanding after his discharge, however, he was given only 1 drop (12,000 units) Afi D₂ forte daily.

Definite deterioration was shown in a radiologic examination on June 20th, 1949, and he was again started on 250,000 units daily, orally. On October 14th, 1949, he was readmitted to the hospital for supervision.

Table 1.

Date	Serum-Calcium Mg%	Serum-Phosphorus Mg%	Serum-Phosphatase Units (Bodansky)	Treatment
8.8.47				<ul style="list-style-type: none"> - Cod liver oil 5 ml × 1 - Cod liver oil 5 ml × 3 - Cod liver oil 10 ml × 3
4.9.47				
11.9.47				
6.10.47				→ Vitamin D ₂ 250 000 I. U. i.m.
30.10.47	10.9	2.8	14.8	→ Vitamin D ₂ 500 000 I. U. i.m.
30.10.47				
19.4.48	11.30	2.2	5.8	→ Vitamin D ₂ 500 000 I. U. i.m.
21.4.48				
20.9.48	11.4	1.8		<ul style="list-style-type: none"> - Vitamin D₂ 140 000 I. U. daily orally - Vitamin D₂ 250 000 I. U. daily orally - Vitamin D₂ 12 000 I. U. daily orally - Vitamin D₂ 250 000 I. U. daily orally
27.9.48				
27.10.48	11.09	3.75	39.2	
9.11.48				
20.11.48	10.69			
24.11.48				
22.6.49				
18.10.49	9.79	4.1	3.8	

At this time he gave the impression of a healthy, alert, normal child, whose height was now 95.5 cm (average normal 96 cm), and his weight was 12.7 kg (2.3 below normal); circumference of the head was 50 cm. A slight "rickety rosary" was still present, together with enlargement of the ends of the bones at the wrists and ankles. There was slight arching of the humerus and ulna on both sides and marked arching of the legs above and below the knees. Neurologic findings were unchanged from previous examination, and the fundus oculi showed no definitely morbid changes. There was considerable improvement in the wrists, and the epiphyseal lines were quite sharply defined—the cup-shaped outlines had practically vanished (Fig. 1 B). The skull, compared with roentgenograms of October 29th, 1948, had become larger—its height, particularly, having increased. The artificial sutures were still open, but they seemed somewhat narrower than they had been on October 29th, 1948.

Laboratory Findings: Figure 1 shows that the serum calcium levels varied between 9.79 and 11.39 mg per cent. Before any radiologically demonstrable improvement was observed, the serum phosphorus levels varied between 1.8 and 2.8 mg per cent. After radiologically demonstrable improvement was observed, there was a rise in the phosphorus

levels—4.1 mg being found at the last examination. The phosphatase varied somewhat, the highest figure of 39.2 being found after radiologically demonstrable improvement had been observed for the first time—the lowest figure being found when considerable improvement was observed.

The urine was acid, and contained neither protein nor sugar. Schlesinger's reaction 1/10 was negative. No formed elements were seen under the microscope and no crystals of cystin were found. Functional tests of the kidney included the concentration test during which the specific gravity of the urine rose to 1033. Non-protein nitrogen was 30.4 mg per cent. Macroscopic and microscopic appearance of the feces were normal. Wassermann was negative. Alkali reserve volume was 55 per cent, icteric index (Meulengracht) was 3—5, thymol was 0.06, and cholesterol 232 mg per cent. Examination of the serum on October 18th, 1949, showed albumin 4.39 per cent, globulin 3.11 per cent, and the albumin globulin ratio 1.41.

Family history:

Except for the patient's mother, there was nothing in the family of significance. There was nothing remarkable about the father's appearance and the parents were unrelated. She had no complaints, and had never suffered from headache, disturbance of vision, or pain in her limbs, but legs had begun to be bowed when she was 2 years old, and had remained so.

On examination (November 23rd, 1948) she was somewhat grey-haired and looked older than her age. Her height was 134 cm, weight 54 kg. Her head (Fig. 3 B) was strikingly high and narrow, with a high, prominent forehead and steep lines on both sides of her head. Circumference of her head was 56 cm. Legs were very much bowed; the gait was waddling; and the wrists and ankles were comparatively thick. No craniotabes or "rickety rosary" was noted, and the remainder of the examination was essentially negative. Liver and spleen were not palpable; reflexes were normal. Fundus oculi seemed normal.

Roentgenogram of the skull (Fig. 2 B) taken from the side showed it to be long and oval dolichocephalic with a high forehead, with the base of the skull showing a straight line from the sinus frontalis to the protuberantia occipitalis. There was a hint of platybasia. Impressiones digitatae increased in the posterior half of the skull, with a slight prominence of the coronary and lambdoid sutures (remarkably small) noted. On the frontal projection the skull was seen to taper off somewhat towards the sagittal suture, which seemed to have undergone synostosis "Keilschädel," scaphocephalic deformity.

The upper and lower limbs were short and clumsy, with large and bulky muscle attachments. Arching of the humerus was present, particularly of the femur on both sides and of the legs below the knees,

with lateral convexity. There was corresponding thickening of the compact bone on the concave side. The outlines of the articular surfaces of the knees and ankles were uneven, and arthritic deposits and subchondral sclerosis (notably in the ankles) could be seen. The pelvis was small and somewhat funnel-shaped.

Urine was acid, light golden-brown, clear, with a specific gravity of 1020. No protein, sugar, nor blood. Schlesinger 1/10+.

Serum calcium was 9.69 mg per cent and serum phosphorus 1.5 mg per cent. Phosphatase 3.5 Bodansky units.

Discussion:

Examinations have failed to show that rachitic changes were due to any disease of the liver, kidney or pancreas, and there was no sign of sprue or celiac disease. The patient did not present any evidence of cystin diathesis, which may be accompanied by skeletal changes resembling rickets. Premature ossification of certain parts of the skeleton is the last thing one would expect to find in a case of rickets, especially in ordinary deficiency rickets. It could be assumed that the simultaneous occurrence of craniostenosis and Vitamin D resistant rickets in this case was accidental. However, this assumption is challenged by the discovery of similar skeletal changes in the mother, whose skull showed signs indicative of a slight degree of craniostenosis and whose arching of the limbs was suggestive of an earlier attack of rickets. There is lack of evidence to prove that the mother suffered from Vitamin D resistant rickets, since she had not been closely examined as a child and was given no anti-rachitic treatment. We know, however, that in some cases of Vitamin D resistant rickets this disorder may stop at puberty (6). It is also noteworthy that the serum phosphorus was found to be low in the mother: 1.5 mg per cent (BULLOCK (7) found that the average in adults is 3.65 mg per cent, with a range of 4.85 to 2.5). It is possible, therefore, that the mother and son suffer from the same disease. CARLGREN (8) has reported a similar case—the mother of a patient who suffered from Vitamin D resistant rickets and presented deformities of the limbs and pelvis, whose blood phosphorus was low (2.8 mg per cent) while the calcium and phosphatase concentration remained within normal limits. There are also other reports of familial D vitamin resistant rickets (9). Several reports also exist of the familial occurrence of craniostenosis either alone or associated with other anomalies.

Summary

The finding of signs indicative of the same combination of conditions in mother and child points to the presence of a hereditary syn-

drome sui generis. The hereditary factor or factors responsible for this syndrome have given rise, on the one hand, to craniostenosis and, on the other hand, to Vitamin D resistance, with consequent rickets.

O. IMERSLUND: *Craniosténose et rachitisme résistant à la Vitamine D.*

La découverte de signes montrant le même ensemble de conditions chez la mère et l'enfant démontre l'existence d'un syndrome héréditaire sui generis. Le facteur ou les facteurs héréditaires responsables de ce syndrome ont donné naissance d'une part à de la craniosténose et d'autre part à de la résistance à la vitamine D, avec comme conséquence, l'apparition du rachitisme.

O. IMERSLUND: *Kraniostenose und Vitamin-D-resistente Rachitis.*

Der Befund von Symptomen, welche dieselbe Kombination von Zuständen bei Mutter und Kind anzeigen, deutet auf das Vorhandensein eines hereditären Syndroms sui generis; Der oder die hereditären Faktoren, auf denen dieses Syndrom beruht, haben einerseits zu Kraniostenose, andererseits zu Vitamin-D-Resistenz mit folgender Rachitis geführt.

O. IMERSLUND: *Cráneoostenosis y raquitismo resistente a la vitamina D.*

El hallazgo de signos evidentes de la misma combinación de enfermedades en la madre y el niño habla en favor de la presencia de un síndrome hereditario. El factor o factores hereditarios responsables de este síndrome ha dado lugar por una parte a la cráneoostenosis y por otra a la resistencia a la vitamina D con el consecuente raquitismo.

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PROCEEDINGS OF PEDIATRIC SOCIETIES

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once even in a child. The troubles which have, as a rule, been extremely moderate have remained considerably longer than the electrocardiographic changes, though mostly disappearing after some months. Even when the changes are marked, the prognosis, apart from isolated cases, appears to be good, judging both clinically, from the electrocardiograms and the functional capacity.

Bo Hellström and Bo Vahlquist: Experimental inoculation of exanthema subitum.

Exanthema subitum is a common eruptive disease, particularly frequent in children at an age of 1/2—3 years. Like rubeola and morbilli, it has probably a virus etiology, though the epidemiology remains obscure. Experimental attempts at ascertaining the infectious agent have, so far, failed. Since the exanthema subitum is an exceedingly benign disease, practically free from any known complications or after-effects, inoculation tests have been performed on human volunteers. In 14 cases of children with cerebral damage or malformation, inoculations have been tried from definite cases of exanthema subitum. On the 4th—5th day of the disease, as a rule the first exanthematous days 2—5 ml. of blood were taken and, with heparin added, given intramuscularly to the subjects. Donors and subjects have been separated in different departments without any possibility to get into personal contact. In 3 cases, the inoculation tests gave definitely positive results with pyrexia of about 3 days' duration, beginning on the 6th—9th day, followed by a fall in temperature and an exanthematous outbreak on the 9th—12th day, simultaneously with a leuko-neutropenia and a relative lymphocytosis. The experiments show that in the exanthematous stage of exanthema subitum the infectious agent is circulating in the blood.

Meeting, January 26, 1951.

Yngve Larsson: Treatment of diabetes with insulin mixtures.

The great variation in the need of diabetic children for insulin necessitates individual consideration in each case. The majority of these patients can be kept under control with a morning injection of

protamine or protamine-zinc insulin. A small group of severe labile cases of diabetes (brittle diabetes) are an exception. They need, as a rule, more than one kind of insulin and, often, several doses daily. The author presents a tabular list of 213 cases of insulin-treated children. To 117, one kind of insulin in one daily dose sufficed. 61 had both rapidly and slowly absorbed insulin in separate injections once a day; 35 had two injections each 24 hours. In labile cases a combination of 2 parts of rapid soluble insulin and 1 part of slow protamine-zinc or protamine insulin is very useful in treatment. The chemical and physiological properties of the insulin mixtures are described. Their effect does not represent a summation of the various components. A mixture produces a satiate insulin protamine of an intermediary effect. Insulin mixtures are not stable for long and have to be prepared afresh for each injection.

The results of treatment of 17 cases of diabetes in children with a 2:1 mixture are described. In 11 cases, the effect was good and in 2 cases doubtful. In one instance, a deterioration was noted. In 3 cases, the effect has as yet not been definitely ascertained. A mixture of 2 parts of rapid and 1 part of slow insulin equals, approximately, 2 parts of slow and 1 part of rapid insulin, when administered in separate injections. In some cases, identical results may be obtained from separate injections as from mixtures. The latter are, nevertheless, to be preferred for practical and technical, as well as for psychological reasons.

H. Enell: A follow-up examination of Calmette vaccinated children.

Since 1944, 35,000 children at the elementary schools in Stockholm have been BCG vaccinated. In 1950 a follow-up examination was initiated at one of the schools. 97.4 per cent of the 1,100 pupils were examined. Excepting the lowest form where no general Calmette vaccination had been carried out 55 per cent of the children were tuberculin positive to the patch test; a further 26.5 per cent were positive to Mantoux 1 mg. and the remaining 18.5 per cent tuberculin negative. In the higher classes the number of tuberculin positive cases was twice that of the lowest form. 79 per cent of all the children were BCG vaccinated. At the follow-up, only 6.9 per cent of these children were tuberculin negative. None of the BCG vaccinated children had ever developed clinical tuberculosis. 26 of the 66 spontaneously positive children had been exposed to their tuberculous infection after beginning school. Only 5 of the 104 children vaccinated in 1945. were entirely tuberculin negative. In the other group also, the post-vaccinal tuberculin allergy is found to remain comparatively long. In these instances, the possibility of a superinfection can, of course, not be excluded, though it is difficult to ascertain.

A. Hellström and K. A. Melin: Glutamine acid treatment in cases of mental retardation.

G. Ekström: Follow-up examination of cases of patent ductus arteriosus operated upon in Stockholm.

R. Krämer: Pulmonary stenosis with auricular septal defect.

35 of our 49 cases of isolated pulmonary stenosis without an overriding aorta had no ascertainable septal defect, 10 had an auricular septal defect and 4 an intraventricular septal defect. In an uncomplicated pulmonary stenosis, the clinical symptomatology forms a limited entity of its own, characterized by a markedly harsh systolic murmur above the pulmonary artery with a thull, and, on X-ray, pronounced bend of a pulsating pulmonary arch and evidently reduced blood supply to the peripheral parts of the lungs. In most of the ECG, a distinct right axis deviation with signs of hypertrophy is found.

5 of the 10 cases of pulmonary stenosis with an auricular septal defect had definite cyanosis at rest, 2 had occasional cyanotic attacks during exercise. The 3 remaining cases were always quite free from cyanosis. During life an acyanotic or cyanotic pulmonary stenosis with an auricular septal defect can be distinguished from the two other forms of benign pulmonary stenosis, or from other complicated cyanotic changes with pulmonary stenosis, only by cardiac catheterization or angiocardiology. Sometimes the cyanotic pulmonary stenosis may very easily be mistaken for a Fallot's tetrad. The differential diagnosis of a pulmonary stenosis with an auricular septal defect is of great practical importance, since it is possible, at present by valvotomy, to operate upon the stenosed pulmonary valves (BROCK) and thus improve the condition considerably.

Th. Ehrenpreis: New aspects on the pathogenesis and treatment of the megacolon.

In 1946, the author was in a position to show, in a clinical and roentgenologic study of the onset and early development of this disease in 10 newborns, that the colon dilatation is missing in the early stage and, therefore, is not the essential feature in the pathogenesis of the disease but a secondary phenomenon. As to the aetiology of the disease, neither these cases nor other reports in the literature gave any definite clue. In 1949, SWENSON, in a series of 20 cases, found that the rectum and part of the sigmoid had no share in the colon dilatation but, on the contrary, remained strikingly narrow. He supposed this narrowing of the intestine to form an obstruction that caused the colon dilatation. A surgical removal of the narrow rectosigmoid resulted in the disappearances of the symptoms. At the same time, WHITE-

HOUSE & KERNOHAN showed that there was a total aplasia of ganglion cells in AUERBACH's and MEISSNER's plexuses in the rectosigmoid. These plexuses in the dilated part of the colon were normal. During the past 2 years, the operation proposed by SWENSON, rectosigmoidectomy, has been performed in 150 cases of megacolon. The results have been extremely good and entirely confirm the correctness of the suggested conception of the pathogenesis of the disease.

A film, demonstrating the operation was shown (10 minutes).

Chr. Lingen: A demonstration of an apparatus for electrophoresis.

Meeting, February 9, 1951.

Erik Jacobsson and Herman Gladnikoff: Hyaluronidase as an aid to urography in children.

An improved method for obtaining adequate urograms, especially in infants and small children, was described. The tissues, at the site of a subsequent injection of contrast medium, were prepared by intramuscular administration of hyalase dissolved in 1/2 per cent Xylocain, in such a way as to render the injection of the contrast medium practically painless and considerably reduce tissue resistance. In addition, dispersion, absorption and excretion of the contrast medium were notably accelerated. In this manner, perfect urograms, fully comparable with those obtained by the intravenous technique, were secured.

I. Bjelkhagen, H. Kristiansen and Y. Lindblad: Retrolental fibroplasia: Follow-up examination of babies born between 1940 and 1949.

After summarising the history, symptoms, etiology and treatment of fibroplasia, an account was given of a follow-up examination of children with a birth weight of less than 2,000 g, admitted to the Samariten Children's Hospital, during the years 1940-49. The investigation comprised 511 children. 182 children had died and 242 were examined. 87 were not available for examination. 3 children (2 boys and 1 girl) had fibroplasia. 2 of these are imbeciles. The birth weights of these 3 children were 1,100-1,390 g. In addition, a description was given of 2 cases, discovered in the Out-Patient Department, with birth weights of 1,580 and 1,830 g. They are mentally normal. The mothers were healthy during the pregnancy. All, except one, were reared, for various lengths of time, in an incubator. 4 of the children were not breast fed and this is a possible etiological factor. 2 of the children were treated with vitamin E without any noteworthy effect. Apart from these 5 cases, a description of a case (from a school for the blind)

of retinal dysplasia, a disease closely akin to fibroplasia was given. Finally, the probable need of an institution, in the near future, for the treatment of such children under school age, was discussed. No such institution, as yet, exists.

S. Jorup and E. Bergquist: The percutaneous tuberculin reaction (patch test) in relation to BCG vaccination.

An investigation of the tuberculin reaction in about 4,250 children, 48 in hospital and the remainder outpatients, showed that the tuberculin patch test on infants is more sensitive than Mantoux 1 mg., particularly in the sick children. Children who have not been vaccinated at birth were tested with the Mantoux test only when the patch test was negative after BCG. A negative patch test but Mantoux 1 mg. positive was noted in 0.7 and 2.5 per cent of the representative groups of the out-patient children up to 7 years of age. The patch test was the only tuberculin test used before the BCG vaccination, among practically all cases. A small number of Mantoux positive cases have, no doubt, been vaccinated but no earlier reaction of the type of "Koch's phenomenon" with abscess formation has occurred, possibly due to the weak allergy. Sick children, or children who were recently ill, were not, as a matter of course, vaccinated, since the level of allergy was likely to have decreased or disappeared. Accurate technique in performing the patch test with a control test and a careful reading are indispensable prerequisites in order to secure most value from the test.

Arne Hultman: Antibiotic treatment of sinusitis in children.

Nasopharyngeal swabs were taken from patients with clinical, as well as roentgenological sinusitis. Sensitivity to the sulfa group of drugs and penicillin was then determined by JENSEN's method. Cases resistant to sulfa, in all 68 patients, were admitted to hospital and treated with penicillin or aureomycin, and, as the only local treatment, Biogan mite (corresponding to Privin, CIBA). In these 68 cases, Hemophilus influenzae predominated (53.6 per cent), followed by streptococcus aureus (16 per cent), pneumococci (8.8 per cent) and B-haemolytic streptococci (3 per cent). The sedimentation rate was usually raised, while the white cell count was normal. Only 7 per cent showed a big enlargement of adenoids on X-ray. 85.3 per cent recovered after 7 to 10 days' treatment. 7.3 per cent were, clinically, considerably improved, while 7.4 per cent remained entirely unchanged. 3 per cent of the latter had deviated septa.

Proceedings of the Pediatric Society of South Sweden

Meeting, February 18, 1951.

Brita Mannerheim: Dermatomyositis treated with cortisone.

A boy, born Nov. 22th, 1941, was demonstrated, prior to cortisone treatment, at the Pediatric Section's meeting in March 1950. The diagnosis of dermatomyositis was established by biopsy. The boy had been treated with paraminobenzoic acid, Doca + vitamin C, Antasten, among other things, without any noticeable effect. Two implantations of calf hypophysis were followed by temporary improvement. Cortisone treatment was instituted Jan. 1951 in the following dosage: Cortone, 50 mg \times 3 the first day, 50 mg \times 2 the second day, 50 mg \times 1 the third day, 50 mg \times 1 every other day for three weeks. The eosinophils were followed during the treatment. Despite the fact that an immediate decline in the eosinophil value after the injections was not always obtained the therapeutic effect was evident. The mobility improved, the weight increased, the sedimentation rate fell, the anemia decreased, etc. Although it appears as if the cortisone treatment had affected a significant change in the morbid picture, one must reckon with in this patient, as in other ACTH treated cases, only temporary good effect.

Vera Oldfelt: Oligophrenic children treated with glutamic acid.

Sixteen children at a mental institution, ranging in age from 7 to 14 years with I. Qs. from 42 to 77, were treated for 4 months with 18 g l(+) glutamic acid, divided into 3 doses. A control group of 15 children of approximately the same age and intelligence level was given a placebo. No significant difference in the I. Qs. was obtained when tested after the treatment except in one case. This subject showed an increase but this rise had already begun before the glutamic acid therapy was instituted. The I. Q. has continued to increase without glutamic acid and should probably be attributed to a change in environment. The treatment does not produce any untoward effects. According to ZIMMERMAN glutamic acid therapy should be given for 6 months or more and be carried out with individually adapted doses, often exceeding those employed in this study. Definite conclusions on the effect of glutamic acid on the I. Q. of mentally defective children therefore cannot be drawn from this investigation.

J. Löfvenberg: Two cases of progressive muscular dystrophy treated with insulin and a carbohydrate-rich diet.

MAYERHOFER (*Excerpta Medica* 4: 483, 1950) has obtained remarkably good results in the treatment of progressive muscular dystrophy

with insulin in small doses together with sugar and a carbohydrate-rich diet. This therapy has been tested at the Children's Hospital in Linköping on two children with this disease. The patients received at first 6 and later 8 I. U. of regular insulin twice daily and in addition ample sugar and carbohydrates. An 11 year old boy with a 2 year history and moderately pronounced symptoms was treated for about 2 months. Some improvement was noted. A 7 year old boy with a 4 year history and a considerably more advanced morbid picture was treated for only 14 days. No improvement was observed during this time.

G. Herlitz: Some cases of hypertension in children.

Case 1. Girl, born 1939, had experienced since the autumn of 1948 occasional night attacks of headache and vomiting, at first at intervals of several months but later more frequently. In the intervening periods she was well. On Jan. 29th, 1950 she was suddenly stricken with severe headache and vomiting, and lost consciousness. When admitted to the Children's Hospital two hours later she could not talk but was otherwise lucid; the left corner of her mouth was strongly drawn up and the left eye was tightly closed in a tonic convulsion. The left pupil was smaller than the right. The blood pressure was 170/110 in the arm and 200/130 in the leg. The following day she was completely lucid and the paralysis was better. She showed papilledema and loss of lateral deviation of the right eye. Urography showed that the left kidney was quite small and it seemed to be deformed. The secretion on the left side appeared to be considerably reduced. A Volhard's test in connection with retrograde pyelography showed normal excretion and also satisfactory diluting and concentrating capacity. The other examinations gave normal findings. The blood pressure varied between 170 and 200 systolic and between 110 and 130 diastolic. Because of this and the fact that the right kidney apparently functioned well a left-sided nephrectomy was performed. Four hours after the operation the blood pressure was around 190/110. Two days later it was 130/100 and it decreased further. Since then the girl's condition has been excellent; the neurological symptoms receded rapidly. No headaches after the operation. The removed kidney was markedly lobulated and exhibited a microscopic picture of a pyelonephritic atrophied kidney.

In 1934 GOLDBLATT succeeded in producing chronic hypertension in dogs through partial constriction of one of the renal arteries. Since the hypertension did not disappear after denervation of the kidney, resection of the roots of the spinal cord, etc., GOLDBLATT concluded that the mechanism was humoral. He assumed that the ischemic kidney secreted a vasoconstrictor and pressor substance. Experiments of HOUSSAY, BRAUN—MENÉNDEZ, and others substantiated this theory.

From these and other investigations the conclusion has been reached that the ischemic kidney liberates renin, a substance which had been discovered in 1898 by TIGERSTEDT, among others. In humans there are several cases known where hypertension resulting from unilateral pyelonephritis has been radically cured by nephrectomy. PICKERING has demonstrated in rabbits, in which hypertension was produced by partial constriction of a renal artery, that if the ischemic kidney is removed after the hypertension has existed for 8 days the arterial pressure falls rapidly; but if the nephrectomy is not performed until after 7 weeks the pressure does not decrease. ASK-UPMARK found that of the 20 or more cases of malignant nephrosclerosis in individuals under 20 years of age, reported in the literature up to 1928, more than three-fourths were girls. In almost every one of these it could be demonstrated that one kidney was smaller than the other. Cases of hypertension in young women should therefore arouse the suspicion of a kidney malformation.

Case 2. Boy, born 1943, ill from infancy. When 4 months old he was admitted to a children's hospital for septicemia and endocarditis. After that he had repeated otitis and nephritis. The facial veins below the eyes had been noticeable since he was 5 years old. After removal of adenoids, in 1947, he had a serious prolonged bleeding. He did not complain of headaches. In Jan. 1951 he was examined at the Children's Hospital in Linköping. There was an increased venous pattern around the eyes with small superficial telangiectases in the face. Cardiac examination showed a harsh systolic murmur maximum over the base. The second heart sound was doubled. The blood pressure in the right arm was 260/0 and in the left 170 to 190/70 to 90; in the right leg 107/50 and in the left 115/95. The retina showed a slight edema with increased convolution and tension of the vessels. An ECG showed nothing abnormal. A roentgenogram of the heart did not show any definite deviation from the normal, but at the lower edge of the fifth ribs there were erosions characteristic of coarctation of the aorta.

The usual site of the stenosis is in the arch of the aorta, distal of the origin of the subclavian artery, but occasionally the stenosis can lie proximally. In the case reported here the pronounced difference in the blood pressure in the right and left arm should surely indicate that the stenosis lies proximal to or at the site of origin of the left subclavian artery. However, it can hardly be located proximally for it must in all probability lie distal of the opening of Botalli's duct. If the stenosis is located distal of the mouth of Botalli's duct in the aorta a collateral circulation is gradually formed in utero. If the stenosis lies proximal of this position the fetus is not effected by it and the collateral circulation need not be formed until just before birth. At this point the demand for collaterals arises very suddenly. For this reason

children with this type of aortic stenosis usually die at a very early age.

Cases 3 and 4. Twin boys, identical, 18 years old. Since 12 years of age they had complained quite often of headaches, but otherwise they were in good health and took part in athletics. When 16 years old their blood pressures were found to be 170/60 and 160/70. At 18 it had risen to 195/60 and 175/60 respectively. The pressure in the legs was 20 mm. higher than in the arms. A clinical examination gave no evidence of any cause for the hypertension. Intravenous urography showed symmetrical kidneys with even contours; the secretion started rapidly and was good from both kidneys. Nothing pathological could be demonstrated in the renal pelvis, ureters or bladder. An ECG showed a wide P-wave (0.1 sec.) but otherwise no pathological signs. The hypertension in these brothers appears to be of the type known as essential. If the headaches are an indication of increased blood pressure it is possible that this condition existed from 12 years of age.

G. Herlitz: Some investigations on circular caries.

A review of some investigations into the type of caries which is characteristic of small children was presented. The lactic acid content of saliva under different conditions and the effect on this of local penicillin application, mouth washing, etc., were studied. It was emphasized that it seems possible to arrest the disease process in cases of wide-spread superficial caries by oral hygiene alone (removal of the plaques several times daily by brushing) and in more severe cases the caries attack seems to be rapidly inhibited by local penicillin treatment.

*Per Selander,
Malmö, Sweden.*

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NEWS AND COMMENTS

Centre international de l'enfance

La cinquième réunion du Conseil d'Administration du Centre International de l'Enfance s'est tenue les 21 et 22 Mai 1951, au Château de Longchamp, à Paris, sous la présidence du Professeur Robert Debré, et avec la participation du Dr. Rajchman (Pologne), Vice-Président, du Professeur Aujaleu, Trésorier, des Professeurs Carneiro, Représen-

tant du Brésil à l'UNESCO, Fanconi (Zurich) Guest (Cincinnati) et Wallgren (Stockholm), ainsi que de M. Arthur Wauters, ancien ministre du Travail en Belgique, Ministre Plénipotentiaire et ancien Directeur Général du CIE, et du Docteur GAUD, Secrétaire Général.

Le Secrétaire Général a donné des renseignements sur les activités du Centre au cours de l'année 1951. En ce qui concerne l'*Enseignement*, le Cours de Pédiatrie Sociale et le Cours de Réadaptation des enfants atteints d'infirmité motrice, celui-ci réservé aux auxiliaires médicaux, fonctionnent actuellement; les deux autres cours prévus, l'un sur les vaccinations contre les maladies contagieuses de l'enfance, l'autre pour médecins spécialisés dans les soins à donner aux enfants atteints d'infirmité motrice, auront lieu pendant le second semestre de l'année, tandis qu'un colloque sur les maisons et villages d'enfants se tiendra à Megève du 27 Juin au 7 Juillet. Les recherches et études se poursuivent par ailleurs ainsi qu'il a été prévu, et comprennent d'une part les activités de la Station Pilote BCG, des recherches immunobiologiques et des études sur la vaccination contre la coqueluche, et d'autre part des études sur la carence des soins maternels, sur la psychologie de l'enfant et sur les Bibliothèques d'enfants.

Au cours de l'année 1952 l'enseignement comprendrait un cours de Pédiatrie Sociale et un cours de Réadaptation des enfants infirmes moteurs pour auxiliaires médicaux, un colloque sur les établissements pour enfants privés de famille, un cours de vaccination par le BCG, un colloque sur les problèmes de l'enfance dans les pays tropicaux, qui se tiendrait en pays tropical et de préférence en Afrique, enfin un séminaire sur l'utilisation des antibiotiques dans les maladies de l'enfance. Le Conseil a approuvé ces projets.

En ce qui concerne les *Etudes et Recherches*, le Conseil a estimé que l'activité de la Station Pilote BCG devrait être étendue et les recherches sur la vaccination anti-coquelucheuse poursuivies, ainsi que les études sur la carence des soins maternels. La reconduction du programme consacré aux études sur la psychologie de l'enfant qui n'ont pas encore été entreprises a été décidée, ainsi qu'une expérience sur les Bibliothèques d'enfants.

Le Président a indiqué que certains pays de l'Afrique et du Moyen-Orient seraient désireux d'obtenir l'aide du Centre, et éventuellement de W.H.O. et de l'UNICEF pour engager une campagne contre le trachome, maladie de l'enfance, contre les conjonctivites saisonnières qui augmentent considérablement la gravité du trachome et contre les mouches qui sont le principal vecteur de ces maladies; ces questions seront soumises à la prochaine réunion du Conseil.

Le Conseil a demandé que des monographies touchant les cours et les travaux du Centre, ainsi que des sujets d'actualité se rapportant aux problèmes du néo-natalisme, de la naissance et de l'enfance soient

publiés en complément du "COURRIER"; il a exprimé l'avis que la formule actuelle de cette revue devrait être maintenue, une place plus grande étant toutefois réservée aux articles de fond et aux analyses intéressant le secteur social.

En ce qui concerne enfin l'Exposition, "la première année de la vie" qui s'est ouverte dans le parc du Château de Longchamp, le Conseil a témoigné sa satisfaction pour son heureuse réalisation et approuvé l'organisation du voyage de cette Exposition à partir du 15 Juillet prochain dans un certain nombre de villes de France et d'autres pays. Déjà Lille, Nancy, Strasbourg, Tours, Tunis et Bruxelles ont demandé à l'accueillir et ont offert de supporter tous les frais de transport et d'exposition.

Acta Pædiatrica 40: 467—468. Sept. 1951.

BOOK REVIEW

Parenteralflüssigkeitstherapie im Kindesalter. Theorie und Praxis. By Emil Polaček, Bibliotheca Paediatrica, Supplement to Annales Paediatrici. Fasc. 50. S. Karger, Basel. Price SFr 17.—

The intense research during the last decades concerning fluid and electrolyte metabolism has made clear the important role, which is played by this metabolism in the physiology and pathophysiology of the human organism. Increased knowledge of this has been followed by more successful therapy and consequently a lowering of the mortality in many severe diseases. In pediatrics this development has been of great importance especially in the treatment of vomiting and diarrhea in infancy and childhood. Formerly the mortality in dyspepsia was terribly high but has now decreased to a few per cent. This favorable progress has resulted primarily from the use of parenteral fluid therapy to compensate water losses, to restore acid-base equilibrium and to reestablish other ion-balances.

The great number of articles on this subject, which have appeared to report this research has made the literature more and more difficult to survey. In his work "Parenteralflüssigkeitstherapie im Kindesalter, Theorie und Praxis" from the I. Universitäts-Kinderklinik in Prag,

Emil Polaček has devoted a careful study to the earlier investigations in this field, and the book has a very extensive bibliography, containing almost 500 references. The author's own experiences serve as a background, largely hidden by the compilation of the review, which dominates the character of the book.

The preponderance of the work lies in the theoretical part, where the physiology and pathophysiology of the body fluids are exhaustively discussed. The amount and distribution of water in the body, water metabolism and requirement and further the metabolism of the most important electrolytes are the main points of the physiology-section. Two special chapters are devoted to the relationship of the pituitary gland and the renal function in infants in these adjustments.

Through this disposition, however, the account of the extra or intracellular body fluid and other topics are split into several chapters, resulting in many useless repetitions. In different sections of this physiologic part reviews on buffer mechanism, pH and osmotic pressure are found in several different chapters. These could have been consolidated in an introductory chapter on some physico-chemical fundamentals.

The second main part is an account of the pathophysiology of the body fluids, and the therapy of disturbances in water-electrolyte balance, especially concerning children. Alterations in the acid-base-equilibrium and the dehydration following vomiting and diarrhea are the chief chapters. Diabetes and renal insufficiency are also treated from this point of view. The outlines of the pathogenesis of edema, the fundamentals of shock and the probable importance of the insufficient adrenal gland in dehydration of the new-born are some other chapters. The presentation is systematic and extensive with diagrams illustrating the text.

The final chapters contain a description of different fluids suitable for parenteral therapy and some discussion of the practical technique.

The critical remarks above are concerned only with details; this study must be regarded as very valuable. The author has solid knowledge of physical and biological chemistry and has apparently studied the literature concerning parenteral fluid therapy in a very exhaustive way. The theoretical part of the book makes it a valuable work for study also by those not primarily interested in pediatrics.

Bo Hellström.

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ACTA PÆDIATRICA

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MIETTINEN, M., On Thrombosis in Children. Acta Pædiat. 39: 267, Dec. 1950.

WILKINS, L., The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. Charles C. Thomas, Springfield. Ill. U. S. A. 1950.

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FROM THE CHILDREN'S CLINIC OF THE UNIVERSITY, HELSINKI.
(CHIEF: PROFESSOR ARVO YLPPÖ, M. D.)

The Weight of the Thymus in Children of 0—2 Years of Age

by

HILKKA TÄHKÄ

In investigations of the adrenals of children of 0—2 years of age, for purposes of comparison with the thymuses the author removed and weighed them at the post-mortem examinations. The weight of this gland differs widely in each case. It was, therefore, also considered important to investigate whether the child's age, the duration, and the kind of disease have any bearing on the uniformity of weight of this gland, especially since, to the best of the author's knowledge, such investigations have never before been carried out on Finnish children. Large thymuses and their possible role in so called "thymus-deaths" (PALTAUF a. o.) have been discussed extensively in medical literature. It was thought this opportunity would be of value in ascertaining whether there is any foundation for such a point of view.

Material and Methods

The results of 309 post-mortem examinations carried out at the Children's Clinic of Helsinki University in 1948—49 are reported. As part of a wide investigation the thymus, the adrenals and, in many instances, the thyroids had been removed and weighed.

In the following, attention has been paid to the increase in weight of the thymus in infants of 0—2 years of age. There were so very few post-mortem examinations on children aged over 2 years that it was not worth while analysing the results.

97 of the infants (47 male and 50 female) were prematurely born and 212 (127 male and 85 female) were full-term.

The thymus was removed by the author in each case, and was separated from the surrounding tissues as completely as possible. After removal, the gland was weighed, to an accuracy of 0.01 g. All weighings were carried out by the author personally, using the same weights and scale throughout, which, on checking, were found to weigh correctly to an accuracy of 0.001 g.

The statistical examination of the results was carried out by Docent Kari Karhunen. The following formulas have been employed in the calculations:

1. The symbols $x_1, x_2 \dots x_k$ and $y_1, y_2 \dots y_l$ denote the quantities measured. Hence,

$$\text{mean value of } x = m_1 = \frac{1}{k} \sum_{i=1}^k x_i,$$

$$\text{mean value of } y = m_2 = \frac{1}{l} \sum_{i=1}^l y_i$$

mean error of the mean value of

$$x = \sigma(m_1) \sqrt{\frac{\sum_{i=1}^k (x_i - m_1)^2}{k(k-1)}} = \sqrt{\frac{\frac{1}{k} \sum_{i=1}^k x_i^2 - m_1^2}{k-1}}.$$

The probability that m_1 deviates from the true value more than $2 \times \sigma(m)$ is 5 %, more than $2.6 \times \sigma(m)$ 1 %, and more than $3.3 \times \sigma(m)$ 0.1 %. It is assumed here that the quantities studied conform with the so-called normal distribution law, and this assumption, in cases like the present, as a rule holds good with sufficient accuracy.

The mean error in the difference of two quantities, m_1 and m_2 , is obtained from the formula

$$\sigma(m_1 - m_2) = \sqrt{\sigma(m_1)^2 + \sigma(m_2)^2}.$$

2. The correlation coefficient between the quantities x and y has been computed from the formula

$$\gamma = \frac{m_{12}}{\sqrt{m_{11} \cdot m_{22}}}$$

in which

$$m_{11} = \frac{1}{k} \sum_{i=1}^k x_i^2 - m_1^2, \quad m_{22} = \frac{1}{k} \sum_{i=1}^k y_i^2 - m_2^2,$$

$$m_{22} = \frac{1}{k} \sum_{i=1}^k x_i y_i - m_1 m_2.$$

Here x_i and y_i , denote the corresponding x and y values, and m_1 and m_2 are the mean values of x and y .

To estimate the significance of the correlation, the quantity

$$t = \sqrt{k-2} \cdot \frac{r}{\sqrt{1-r^2}}$$

is employed.

The probability that the correlation found is significant can be obtained with the aid of t and k from the special table (so-called t -distribution).

3. The angle coefficient of the regression line illustrating the rectilinear dependence of y on x is

$$b_{21} = r \sqrt{\frac{m_{22}}{m_{11}}}$$

In estimating whether b_{21} deviates from the given value β_{21} the following expression can be formed

$$t = \sqrt{\frac{m_{11}}{m_{22}} \cdot \frac{k-2}{1-r^2}} (b_{21} - \beta_{21})$$

upon which study can be made, with the aid of the t -distribution table, of whether the value obtained differs significantly from zero.

If k is high, $t > 3.3$ corresponds to a 0.1 %, $t > 2.6$ to a 1 % and $t > 2$ to a 5 % probability of error in the conclusion that t deviates significantly from zero.

4. Denominations corresponding to agreed probability of error percentages, p , are often employed as follows:

The difference observed is almost significant, if 1 % $\leq p < 5$ %

» » » » significant, if 0.1 % $\leq p < 1$ %

» » » » highly significant, if $p < 0.1$ %.

Changes in the weight of the thymus

Foetal development

CLATWORTHY & ANDERSON (1944) described the increase in the weight of the thymus in the foetus. Their results are based on the values of JACKSON and SCAMMON, and on values collected by JACKSON from the literature. The weights of the thymus in fetuses of 75—2500 g, published by EKHOLM & NIEMINEVA from Finland, coincide fairly well with the values given by CLATWORTHY & ANDERSON. Of

their results, the weights of the thymus of foetuses from the immature stage (birth weight 600—1249 g) onwards are particularly interesting in this connection (Table 1).

Table 1.

The weights of the thymus in foetuses weighing 600—2500 g, according to EKHOLM & NIEMINEVA.

Weight of foetus (g)	Number of cases	Absolute weight of thymus (g)	Relative weight of thymus (%)
600—1 249	14	1.75—3.02	1 : 412 or 0.24
1 250—2 500	16	3.8 —9.1	1 : 306 or 0.32

EKHOLM & NIEMINEVA particularly stress that the individual variations in the weight of the thymus are remarkably great.

Changes in the weight of the thymus after birth

Table 2 shows the average weights of the thymus of newborn infants according to several investigations.

Table 2.

The weight of the thymus in newborn infants.

Author	Weight of the thymus (g)			Relative weight of the thymus (%)		
		Male	Female		Male	Female
E. BOYD	13					
BRATTON	11.18	11.77	10.40	0.345		
CASTALDI & VANNUCCI ..		13.09	10.22			
FONTANA	12.5					
FRIEDLEBEN	13.98					
GREENWOOD & WOODS ..	10.26					
HAMMAR	13.2					
RÖSSLE & ROULET		12.57	10.93			
V. SURY.....	12.9					
UOTILA		8.83	8.50		0.262	0.252

HAMMAR, E. BOYD, YLPPÖ, etc., have indicated that the weight of the thymus varies noticeably with the individual, and that many

injurious factors cause a decrease in its size. On account of this, reports in the literature on the size of the thymus vary tremendously. According to HAMMAR, the average weight of the thymus is:

	Average value (g)	Range (g)
In infants	17.2	7 —25
In children of 1—5 years.....	23	8.5—49

The corresponding figures according to FRIEDLEBEN are:

Age	Average value (g)	Range (g)
1—9 moths	20.13	9.74—34.10
9 months—2 years.....	26.60	19.97—37.72

On the basis of HAMMAR's, v. SURY's, BRATTON's and her own investigation BOYD calculated the average weight of the thymus in infants of different ages in good nutritional condition who had died suddenly (duration of disease 0—2 days). Similarly, on the basis of v. SURY's, FRIEDLEBEN's, v. METTENHEIMER's, BOVARD & NICOLL's and her own investigations, she calculated the average weight of the thymus in under-nourished children who had died after a disease of long duration (Table 3).

Table 3.

The average weight of the thymus in infants of different ages.

Age	Average weight of thymus (g)	
	Acute cases	Chronic cases
Newborn	13	
0—1 months	13.3	5.9
1—2 "	18.4	6.0
2—3 "	22.1	6.5
3—4 "	25.5	6.2
4—5 "	19.3	6.3
5—6 "	18.6	4.7
6—12 "	22.0	5.1
1—2 years	24.2	4.6

In BRATTON's material, thymuses in boys up to 4 years of age are comparatively larger than in girls. The other authors mentioned above were not able to find a distinct difference between the sexes.

As to the development of the weight of the thymus in premature infants, no mention has been found in literature.

Present Investigations

Full-term infants

Table 4 shows the average value of the weight of the thymus in full-term infants, classified according to age.

Table 4.

The weight of the thymus in full-term infants in different age-groups.

Age	Weight of thymus (g)		Number of cases
	Average	Range	
0—7 days	6.47 ± 0.95	2.21—28.05	21
8—14 "	5.02 ± 0.98	0.91—10.71	12
15—30 "	4.53 ± 0.86	0.90—11.00	16
1—2 months	4.10 ± 0.76	0.95—13.50	17
2—3 "	3.97 ± 0.63	0.60—13.30	29
3—4 "	4.27 ± 0.78	0.90—13.05	19
4—5 "	7.43 ± 1.70	0.90—28.45	22
5—6 "	5.69 ± 0.97	0.95—14.22	16
6—9 "	8.46 ± 1.50	1.15—28.55	26
9—12 "	7.75 ± 1.78	1.90—15.82	12
12—24 "	8.17 ± 1.43	0.50—21.50	16

It is not possible from Table 4 to draw any conclusions worth mentioning on the changes in the weight of the thymus, the individual variations being so great. If these results are compared with the average weights in Table 3, of children who have been ill for a long time, it will be found that the values are very similar.

No significant difference in the weights of the thymus in male and female children can be shown.

Premature infants

Table 5 shows the weights of the thymus in premature infants.

Table 5.

The weight of the thymus in premature infants.

Age	Weight of thymus (g)		Number of cases
	Average	Range	
0—7 days	3.22 ± 0.33	0.60—12.93	48
8—14 "	2.32 ± 0.40	0.82—3.81	12
15—30 "	1.22 ± 0.24	0.35—2.10	7
1—2 months	1.17 ± 0.32	0.20—4.60	13
2—3 "	2.17 ± 0.60	0.35—4.43	7
3—4 "	1.42 ± 0.20	0.47—2.08	7
4—5 "	3.00 —	1.90—4.00	2
5—6 "	— —	— —	—
6—9 "	3.38 —	— —	1

Noticeable variations in weight are also to be found in the thymuses of premature infants in single cases, even if the absolute weights in these cases are generally smaller.

Birth-weight in correlation to weight of the thymus

CLATWORTHY & ANDERSON, YLPPÖ and others have found that the thymus increases considerably in weight during the last weeks of pregnancy. It was, therefore, considered worthwhile examining whether any correlation exists between birth-weight and weight of the thymus. Table 6 is arranged so that

Table 6.

Relationship between birth-weight and weight of the thymus.

Birth-weight (g)	Average weight of thymus		Number of cases
	Weight in grams	Relative weight (%)	
600—1 249	1.88 ± 0.28	0.19	6
1 250—1 999	5.88 ± 0.73	0.36	4
2 000—2 500	8.46 ± 1.55	0.40	4
over 2 500	12.03 ± 5.31	0.46	4

in each group only those who died during their first day of life are considered; thus the involution of the thymus caused by disease etc. should exert no influence.

It is evident that the absolute and relative weights of the thymus (Table 6) rise considerably during the last weeks of pregnancy. It is not, however, possible to prove this statistically due to the small number and the great variations in the weights in individual cases. As an example of this—the group “above 2500 g” includes the following weights: 8.60, 5.35, 5.95 and 28.05 g.

The Influence of Various Factors on the Size of the Thymus

The most different external factors influence the size of the thymus to a very great extent (HAMMAR). In 1908, JONSON proved, with laboratory animals, that a 9 days' complete fasting causes a reduction in the size of the thymus to 1/4 of its original size. In particular the lymphoid tissue disappears. A chronic condition of under-nourishment causes a decrease in the weight of the thymus to 1/30 of its original size. YLPPÖ has found that the size of the thymus correlates to the nutritive condition of the child: “Thymus is as thick as the subcutaneous fat tissue on the child's breast.”

SELYE has shown in the “General Adaptation Syndrome” theory on the resistance mechanism of the organism that also in the thymus typical changes are to be found in different phases: An alarm reaction causes a rapid decrease in the weight of the thymus, especially the lymphoid tissue. During the stage of resistance the thymus shows a tendency to return to its former size. In the stage of exhaustion it decreases again rapidly.

Size of the thymus in various diseases

BOYD, HAMMAR, SELYE, KEILMANN, etc., have proved that the size of the thymus decreases particularly rapidly due to the most varying diseases. Even a disease of 24 hours' duration is of great importance. Table 3 shows an evident difference in the average weights of the thymuses of children who died from an acute disease and of those who died from diseases of longer duration.

On the other hand, there are, in the literature, frequent references to enlarged thymuses. In 1889, PALTALF put forward a theory on the so-called Status Thymicolymphaticus. According to this theory, the large thymus is often the principal cause of death in a child dying suddenly.—Much has been written on this subject, both for it—SCHRIDDE,

CARR, etc.—and against it—V. SURY, HAMMAR, E. BOYD, etc. HAMMAR emphasizes the fact that in infants who have died suddenly a thymus of normal size might be found, but that this is often explained as being abnormal because at autopsies small, involuted thymuses are usually discovered.

W. BOYD supposes that the so-called “thymus-death” is largely due to an insufficiency in the adrenals. According to him, children who have large thymuses also often have hypoplastic adrenals. KEILMANN, SPOLVERINI etc. have not been able to show any such correlation, but CARR supports BOYD's opinion. WEGELIN has often found a large thyroid gland in children belonging to the Status Thymicolymphaticus group.

RASO has discovered a large thymus in children with anencephalus. According to GROLLMAN a large thymus is often found also in the following diseases: thyreotoxicosis, ADDISON's disease, acromegalia, rickets, myasthenia gravis, leucemia. In UOTILA's material, congenital goitre patients have a thymus somewhat larger than the average.

Present Investigations

The influence of the duration of the disease on the size of the thymus.

Table 7 shows the weights of the thymuses as a function of duration of disease. Premature infants have been excluded because in most cases their age equals the duration of disease.

Table 7.

Weight of the thymus as a function of the duration of disease in full-term infants of 0—2 years of age.

Duration of disease	Weight of thymus (g)		Number of cases
	Average	Range	
0—3 days.....	11.61 ± 1.35	0.90—28.55	32
4—7 ”.....	7.31 ± 0.86	2.21—26.04	34
8—14 ”.....	6.94 ± 1.07	1.11—25.15	26
15—30 ”.....	3.93 ± 0.55	0.90—15.85	36
1—2 months.....	4.00 ± 0.57	0.91—13.50	35
2—3 ”.....	3.26 ± 0.56	0.60—9.00	19
3—4 ”.....	3.30 ± 0.74	1.00—8.41	9
4—5 ”.....	4.58 ± 0.85	1.03—9.60	8
over 5 ”.....	4.24 ± 1.02	0.50—16.32	13

Since the size of the thymus is said to be correlated to the nutritive condition (HAMMAR, YLPPÖ, JONSON, etc.), it was considered important to examine the weights of the thymuses in infants suffering from diarrhoea, such infants generally being in a nutritive condition inferior to that of infants who died from other diseases.

Seventytwo infants died from gastroenteritis. For comparison a so-called miscellaneous group has been employed, comprising all the other groups of diseases. The youngest infant who died from diarrhoea was 15 days old. Consequently, for reasons of unanimity, all cases where the child died at an age of less than 15 days have been omitted from the miscellaneous group. Table 8 shows the weights of the thymuses in the diarrhoea and the miscellaneous group.

Table 8.

Weight of the thymus as a function of the duration of disease in gastroenteritis and the miscellaneous group.

Duration of disease	Weight of thymus (g)		Number of cases	
	Gastroenteritis	Miscellaneous	G—e.	Misc.
0— 3 days	12.77 ± 1.61	17.60 ± 2.52	8	9
4— 7 "	8.95 ± 2.25	9.21 ± 1.40	10	10
8—14 "	5.34 ± 1.24	10.02 ± 2.80	9	8
15—30 "	3.52 ± 0.64	4.53 ± 0.90	18	18
1— 2 months....	3.38 ± 0.80	4.59 ± 0.85	17	18
2— 3 "	2.40 ± 0.71	3.76 ± 0.81	7	12
3— 4 "	1.47 —	3.82 ± 1.02	2	7
4— 5 "	— —	4.58 ± 0.85	—	8
over 5 "	0.50 —	4.52 ± 1.06	1	12

An examination of the results in Tables 7 and 8 shows that the size of the thymus evidently decreases rapidly with the duration of disease. In the miscellaneous group the average weights of thymus reveal no considerable variation, however, in children who have been ill more than 14 days. In the gastroenteritis group the weight of the thymus decreases throughout.

Calculuses of correlation show no significant difference between the weights of the thymuses in diarrhoea and miscellaneous groups. This may be due to the great individual variations in the weights of the thymus.

As Table 4 shows, age has no very great influence on the weight of the thymus. It is probable, therefore, that the above results in the weights of the thymuses are consequences of diseases and of deterioration in nutritive condition.

The "Thymus-Death" in relation to the present material

None of the patients examined suffered the so-called "thymus-death." Clear signs of infection were found in clinical examinations or at least at autopsies, in every patient who had been ill for a short time. The largest thymus found weighed 28.55 g, and it was removed from a child who was in good nutritional condition and who died from pneumonia after two days' illness. A thymus of this size is somewhat larger than the "normal" maximum limit given by HAMMAR, but according to FRIEDLEBEN it ought to be considered as a normal one. Neither were any hypoplastic adrenals found in connection with large thymuses as is evident from investigations into size of the adrenals (TÄHKÄ).

Some special groups

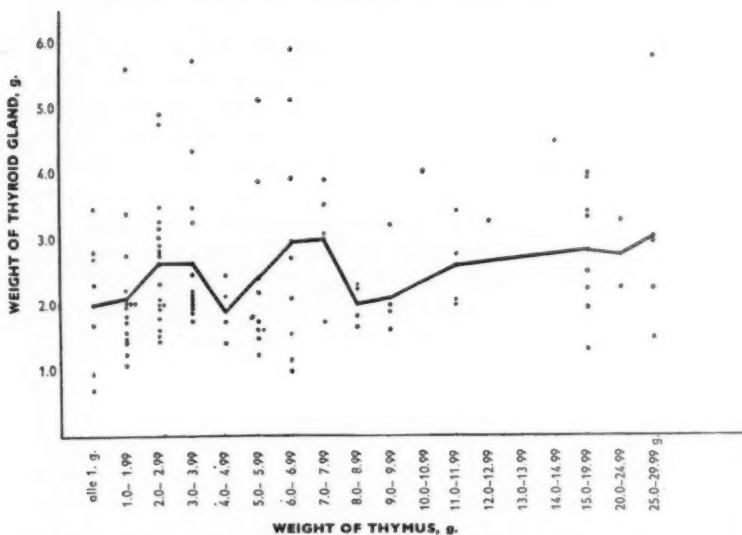
The material included only one case of anencephalus in which the infant weighed 2510 g and survived only 20 minutes. This child had a rather large thymus; the weight being 28.05 g and the relative weight 1.11 per cent.

Quite a number of the patients examined were found to suffer from rickets, which, according to GROLLMAN, may cause an enlarged thymus. No correlation can be proved between rickets and the weight of the thymus, for thymuses of varying sizes were found in those children suffering from rickets.

3 patients died from leucemia in bad nutritive condition. All these patients had rather small thymuses (weights: 1.03, 5.12 and 4.84 g).

Correlation between the Weights of the Thymus and the Thyroid Gland

In 244 cases, the thyroid gland has been weighed. Graph 1 shows the correlation between the thymus and the thyroid gland in full-term children. It appears as if large thymuses are correlated to somewhat higher weights of the thyroid gland, and the calculus of correlation show that the rise in Graph 1 is significant.



Graph 1: Ratio of the weights of the thymus to the thyroid gland.

Congenital goitre

In 10 cases the patient was suffering from congenital goitre. These cases are classified in Table 9.

When comparing weights of the thymus in Table 9 with the weights of the thymus in Tables 4 and 7, it is obvious, that no significant exceptions from the average are found, apart from

Table 9.

The weights of the thymus in cases of congenital goitre.

Case No.	Age	Duration of disease	Diagnosis	Weight of the thyroid gland (g)	Weight of the thymus (g)
183/49	20 min.	20 min.	Anencephalus	8.73	28.05
130/49	5 days	5 days	Vitium cordis cong.	6.54	7.83
100/49	11 "	1 "	Septicemia	7.50	0.90
53/49	28 "	28 "	Hematoma subdurale	6.36	2.22
146/49	1 month	1 month	Vitium cordis cong.	8.02	13.50
354/48	2 $\frac{1}{2}$ months	1 $\frac{1}{2}$ months	Gastroenteritis	7.60	2.20
113/49	2 $\frac{1}{2}$ "	2 $\frac{1}{2}$ "	Vitium cordis cong.	15.82	5.80
400/49	5 $\frac{1}{2}$ "	5 "	Tub. miliaris	27.50	3.77
11/49	5 $\frac{1}{2}$ "	5 $\frac{1}{2}$ "	Debilitas cong.	19.72	4.83
135/49	5 $\frac{1}{2}$ "	8 days	Pneumonia	6.58	8.77

case 183/49 (the child who had anencephalus). There seems, therefore, to be no correlation between the weight of the thymus and the size of the diseased thyroid gland.

Comment

As has been stated above, individual variations, various diseases, and other factors cause considerable changes in the size of the thymus. This explains why the average weights of the thymus put forward by several authors vary. A comparison of the results arrived at with the weights of the thymus given by HAMMAR in his comprehensive investigations reveals that the thymuses in the present material have generally been particularly small. Some authors, however, consider the "normal weights" in HAMMAR's papers rather high. UOTILA gives the average weight of the thymus in Finnish newborn babies as 8.5—8.8 g, the corresponding figure in HAMMAR's material being 13.2 g. Moreover, illnesses of even short duration cause a noticeable decrease in the size of the thymus (JONSON, SELYE, HAMMAR, etc.). On account of this it is not possible to consider any of the results in this material as normal, the child having

suffered in every case from some disease for at least 12—24 hours before death.

Evidently the weight of the thymus is proportional to the nutritive condition of the child. The chronic state of hunger and continual loss of weight explain the fact that in children, who have suffered for a long time from diarrhoea, the size of the thymus is more below average than in children who have died from other diseases.

Summary

1) The thymus of 309 children of 0—2 years of age, who died from various diseases, has been weighed at autopsy.

2) The individual variations in the size of the thymus are fairly great; in full-term infants 0.50—28.55 g, and in prematurely born children 0.20—12.93 g. Age has no clearly discernible influence on the weight of the thymus.

3) During the last weeks of pregnancy the thymus seems to increase to some extent.

4) There is no difference in the size of the thymus in relation to sex.

5) The weight of the thymus decreases rapidly with prolongation of the duration of the disease. The size of the thymus is evidently to a great extent in proportion to the nutritive condition of the child. Consequently, the smallest thymuses are found in children who have died from chronic gastroenteritis.

6) There were no cases of the so-called "thymus-deaths".

7) The average weights of thymuses and thyroid gland increase proportionately.

Le poids du thymus chez les enfants de 0 à 2 ans.

1) Les thymus de 309 enfants âgés de 0 à 2 ans, morts de maladies diverses ont été pesés à l'occasion des autopsies.

2) Les variations individuelles dans le volume du thymus sont relativement grandes: chez des nouveaux nés à terme 0.50—28.55 g, chez des enfants prématurés 0.20—12.93 g. L'âge n'a pas d'influence nettement discernable sur le poids du thymus.

3) Le thymus semble grossir quelque peu pendant les dernières semaines de la grossesse.

4) Il n'y a pas de différence dans la grandeur du thymus en relation avec le sexe.

5) Le poids du thymus décroît rapidement en fonction de la prolongation de la durée de la maladie. Les dimensions du thymus sont évidemment en rapport étroit avec l'état de nutrition de l'enfant. En conséquence, c'est chez les enfants morts de gastroentérites chroniques qu'on trouve les thymus les plus petits.

6) Dans le matériel examiné on n'a trouvé aucun cas dit de "mort thymique."

7) Les poids moyens des glandes thymiques et thyroïdiennes augmentent proportionnellement.

Über das Gewicht der Thymusdrüse bei Kindern von 0—2 Jahren.

1) Das Gewicht der Thymus von 309 Kindern im Alter von 0—2 Jahren, die an verschiedenen Krankheiten gestorben waren, wurde bestimmt.

2) Die individuellen Variationen der Thymusgrösse sind ziemlich bedeutend: bei ausgetragenen Kindern 0,50—28,55 g, bei prämaturren 0,20—12,93 g. Das Alter hat keinen deutlich erkennbaren Einfluss auf das Gewicht der Thymus.

3) Während der letzten Wochen der Schwangerschaft scheint die Thymus etwas zuzunehmen.

4) Es besteht kein Unterschied in der Thymusgrösse zwischen den Geschlechtern.

5) Das Gewicht der Thymus nimmt mit Verlängerung der Krankheitsdauer rasch ab. Die Grösse der Thymus steht offensichtlich in grossem Ausmass im Verhältnis zum Ernährungszustand des Kindes. Dementsprechend wurden die kleinsten Thymusdrüsen bei Kindern gefunden, die an chronischer Gastroenteritis gestorben waren.

6) Das vorliegende Material enthält keine Fälle von sog. „Thymustod“.

7) Die Durchschnittsgewichte der Thymus und der Schilddrüse nehmen proportional zu.

Sobre el peso del timo en niños de edad entre 0—2 años.

1) Se han hecho estudios sobre el peso del timo de 309 niños de edad comprendida entre 0—2 años muertos de enfermedades diversas.

2) Las variaciones individuales en cuanto a tamaño del timo eran las siguientes: en los niños nacidos a término de 0,5—28,55 g y en los prematuros 0,20—12,93 g. La edad no ha mostrado una influencia evidente en lo que hace referencia al peso del timo.

3) Durante las últimas semanas del embarazo parece que hay un aumento evidente del peso de esta glándula.

4) No se han encontrado diferencias en cuanto al peso en relación con el sexo.

5) El peso del timo disminuye rápidamente en las enfermedades de prolongada duración estando en relación evidente con el estado de nutrición del niño y por consiguiente los timos mas pequeños se encuentran en los niños muertos de gastroenteritis crónica.

6) El material estudiado no comprendía casos de la llamada "muerte tímica."

7) El promedio de peso del timo y del tiroides aumenta proporcionalmente.

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FROM THE CHILDREN'S CLINIC IN HELSINGFORS, CHIEF: PROFESSOR ARVO YLPPÖ; THE CHILDREN'S DEPARTMENT OF THE MARIA HOSPITAL, CHIEF: DR. P. HEINIÖ; AND THE PEDIATRIC CLINIC OF THE UNIVERSITY OF TURKU, CHIEF: PROFESSOR T. SALMI.

The Skeletal Age in Diabetic Children

by

G. A. HERNBERG and P.-E. HEIKEL

Disturbances in the carbohydrate metabolism affect almost all endocrine glands, hence diabetes may be thought to cause various reactions in the endocrine system. They do not seem to be particularly marked, however, judging from the general clinical impression of diabetics. The organism is probably able to compensate for such a disturbance for a considerable time. On the other hand, that manifest disturbances in the carbohydrate metabolism do occur in connection with endocrine diseases is a well-known fact. Changes in the hypophysis and in the adrenals are occasionally found in diabetes. As some of the secretions of these glands also influence the bones to a great extent, the growing skeleton, which is under the control of hormones, might be supposed to show some abnormal variations in diabetes mellitus.

The growth of diabetic children has been studied by many workers (TISCHLER and MACKLEN; BROWN and THOMPSON; BOYD and KANTROW; ENGEL, and others). Retarded growth seems to have been very common before the advent of insulin when children were kept on a very strict diet. It was mainly attributed to malnutrition and acidosis, and not to endocrine disorders. In a more recent investigation (WAGNER, WHITE and BOGAN, 1942), disturbed growth was also observed in 118 of 1,407 diabetic children. More than half of them had evidence of hypopituitary infantilism and about one-third a transitory infantilism. Like JOSLIN, TISCHLER and his co-workers con-

sider that diabetic children are on an average taller and sexually more developed than normal in the early stages of the disease but grow more slowly than normal children during the later stages. In some cases, especially if the onset of the disease has occurred in early childhood, hepatomegaly, infantilism and dwarfism may occur. Solitary cases of marked overgrowth in young diabetics have been reported (ENGEL). It is also well-known that, in general, babies born to diabetic mothers are large. Thus, disorders which seem to be of endocrine origin may sometimes affect the growth of diabetic children.

The stature is, however, a poor measure of the rapidity of the skeletal growth. A better impression of the stage of skeletal development is obtained by observing whether infantile proportions still persist. The most reliable results are, however, obtained by roentgenological study. During the growth of the skeleton, there appear, in the x-ray picture, bone centres which finally merge with the diaphysis; this occurs at a fairly definite period in each bone. A skeletal age in each patient can be determined on the basis of the number of bone centres and their union with the diaphysis which, in normal children, coincides with a certain physiological variation in width and with the patient's true age. A shift in the roentgenological skeletal age can thus reveal disorders in the skeletal growth.

BOGAN seems to be the only author who has determined the skeletal age in diabetic children. She examined 169 diabetic children according to Flory and Todd's method, but only by means of x-ray pictures of the hand, and observed a retarded growth of more than 6 months in about 55 per cent, an accelerated growth in about 14 per cent and a normal skeletal age in only 30 per cent (\pm 6 months). There is retarded growth in boys when the disease has lasted more than 13 years and in girls when the disease has lasted more than 9 years. A retardation of more than 2 years occurred in 20.7 per cent. BOGAN does not give an explanation of these results. These figures are of limited value since the normal width of variation is arbitrarily chosen at 6 months, and this is a shorter period than the method allows.

In the present investigation we have studied the skeletal age of diabetic children by a more precise method. Eighty-one diabetic children, 35 girls and 45 boys between the ages of 9 months and 15 years were examined.

The skeletal age was determined on the basis of x-ray pictures of all secondary bone centres in the extremities on the right side. Thirty-two normal children between the ages of 5 and 15 years were examined as a control. Four different methods were used: i.e., those of ELGENMARK, RUCKENSTEINER, LURIE et al. and CAFFEY; the results were checked according to SCHINZ et al.'s method.

ELGENMARK'S method gives the most reliable results and the smallest width of variation, but it is suitable only for children under 5, for boys and girls separately. In it, the great difference in the development of the bone centres in the two sexes is observed. As the method is adopted for children in Sweden, it is more suitable for Finland than the other methods. RUCKENSTEINER'S method requires much time and gives the greatest variation in width; it can be used for all ages ranging from the newborn to the adult, but it is not designed for the two sexes separately. CAFFEY'S method which is a combination of various parts of other methods is designed for boys and girls separately but is not suitable for children over 14 as the results are unreliable even at the age of 10. LURIE et al. have a simple method. It is suitable for the two sexes separately, and the variation width is small. It is based on all bone centres in the right extremities, and can be used for children of 2 1/2 years to adults. However, the border between the different age groups is based, in the majority of the cases, only on one bone centre, and this may lead to incorrect determinations. The method of LURIE et al., when combined with ELGENMARK'S is probably the best. SCHINZ et al.'s resembles that of LURIE et al. but does not take into consideration the difference between the sexes or the great extent of the variability of the separate bone centres. It is inferior to ELGENMARK'S in the youngest age groups. Methods, based on the occurrence of bone centres only in the hand or the foot (TODD, FLORY; VOGT and VICKERS), are not reliable.

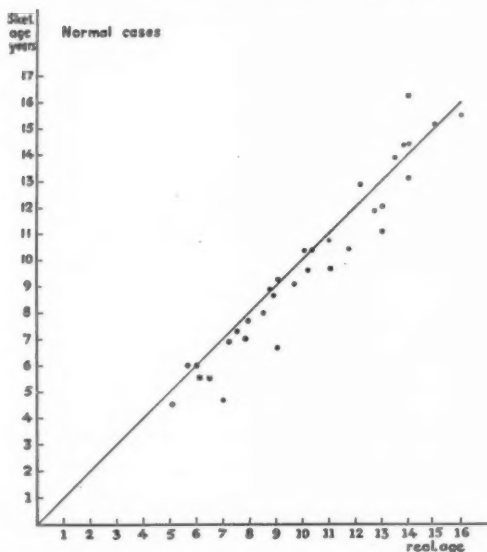


Fig. 1. The relationship between the skeletal age and the patients real age in normal cases.

Determination of the skeletal age is made more difficult owing to the great variability in the first appearance of the bone centres and their union with the diaphysis. The degree of variation in the different bone centres may be between 2 and 10 years. The greater the number of bone centres taken in consideration in the determination of skeletal age, the more exact is the result. But even if all the secondary bone centres of the extremities are taken into account, as in this investigation, the skeletal age can be determined only to within 2 or 3 years. In order to obtain a more exact skeletal age, the mean of the results obtained with the various methods was calculated. This procedure, which is not quite correct mathematically, makes it easier to evaluate the results.

The dispersion in our cases is given in Figs. 1 and 3. The degree of variation in the normal group is ± 2 to 3 years. A deviation of more than ± 1 year from the theoretical skeletal

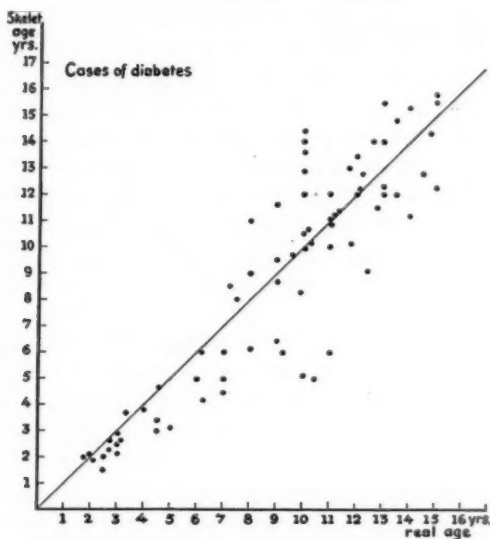


Fig. 2. The relationship between the skeletal age and the patients real age in cases of diabetes mellitus. Note that there is a considerable dispersion on each side of the median line.

age was found only in 10 per cent of the cases, hence ± 1 year was chosen for the normal border.

A graphical presentation of the relationship between the skeletal and the true age in all the diabetics examined is given in Figs. 2 and 3. The skeletal development seems to be normal or slightly decreased up to the age of 7. Later the results are more difficult to interpret as great retardation, acceleration, and numerous normal values were found. In Fig. 3 the dispersion and the distribution of the number of cases according to the groups of deviation are given. The distribution is symmetrical and normal, but the dispersion is somewhat greater than in the normal cases. Setting out from the normal border ± 1 year, retarded growth was observed in 16 cases (20 per cent), 11 boys and 5 girls, and an acceleration in 13 (16 per cent), 5 boys and 8 girls.

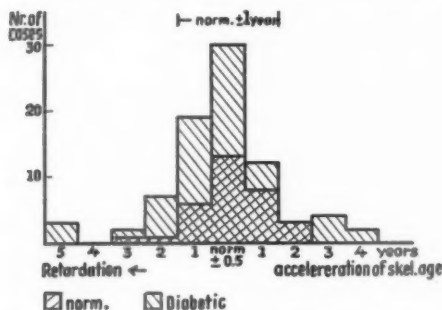


Fig. 3. The degree of variation in the retardation and acceleration of skeletal maturation in normal and diabetic cases. There is a small group with marked retardation and marked acceleration in the diabetic cases, which is not found in normal cases.

Alimentary factors and acidosis are considered the most important non-endocrine factors which may effect the skeletal development. The children's diet was not restricted, excepting the intake of sugar. They were not undernourished.

Acidosis occurred in various degrees during certain periods in several children. The patient was included as a case of acidosis only if acidosis had been present at least for one or two weeks during some period of the disease, and/or attacks of diabetic coma had occurred. The degree and duration of acidosis was difficult to assess and very probably varied a lot in the different subjects. Twenty-eight cases were referred to this rather heterogenous group. The skeletal growth was retarded in 10 cases and in the other 18 the development was normal.

The greatest *retardation* was found in 3 patients of about 10 years of age, where the skeletal development suggested 5 years. The onset of the diabetes had been between 4 and 6 years of age. They seemed to be of normal intellect, 5 to 6 cm below the average height of their age group and, in relation to their age, the proportions were infantile. The liver was in each case palpated 2 to 4 inches below the costal margin. All the children were 9 to 12 kg below the average weight. One child had once been treated for pre-coma; in others according to information, acidosis had not occurred.

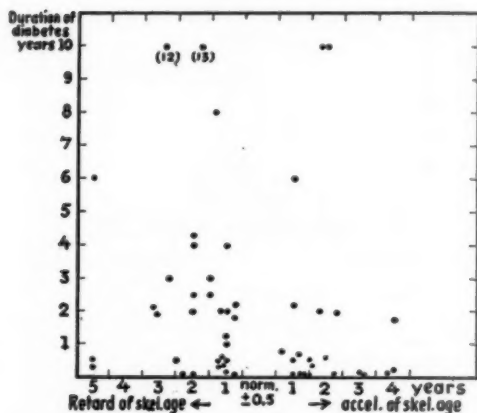


Fig. 4. The relationship between the duration of diabetes mellitus and changes in skeletal age. The changes are not dependent on the duration of the disease.

The greatest *acceleration* in growth observed was 4 years; these patients were also about 10 years old, on an average 12 cm over the average height and 10 to 15 kg over the average weight. The duration of the disease had been short. No family history of diabetes. Acidosis was not mentioned in the past history. In one case there was signs of premature development of the penis. Their intellect was normal.

The *duration* of the disease and its relation to the skeletal age is shown in Fig. 4. There was no evidence of the duration influencing the skeletal age, not even in the cases with marked retardation or acceleration. The divergences from the normal were fairly small in many patients with well controlled diabetes of long duration.

The *stature* of the children were, especially after the ages of 10, generally somewhat above the average of their age (according to YLPPÖ's tables of Finnish children). Only 17 were slightly below the normal; the majority of these had had periods of acidosis. The deviation from the normal occurred just as often in girls as in boys. No connection was found between the height and the duration of the disease.

Discussion

It seems as if the bone age in a certain per cent of diabetic children was retarded especially in connection with hepatomegaly and/or acidosis. In cases with hepatomegaly an increased destruction of sex hormones by the liver is to be suspected. As a matter of fact, the excretion of 17-ketosteroids in cases with hepatomegaly is very low (WHITE). This decrease of the sex hormones would, in these cases, be the cause of the retarded skeletal development.

An accelerated maturing seemed to occur in a small number of the diabetic children of 10 to 15 years of age if the duration of the disease had been short. We may ask, in these cases, whether both the diabetes and the acceleration of the skeletal age were primarily due to accelerated secretion of the hypophysis. Secondly, there may have been increased secretion of sex hormones influencing the growth of bones. WHITE has found that in young diabetics the excretion of 17-ketosteroids at the onset of the disease is in the region of the upper limit of the normal.

Very often skeletal maturation is accelerated in the pre-pubertal period in children, shortly after the onset of diabetes. In 16 cases, where the diabetes developed in the years immediately before puberty and where the child was examined a short time after the onset of the disease, there was an accelerated enchondral skeletal growth. The stature was higher, which coincides with the observations of JOSLIN et al. and TISCHLER et al., but even the skeletal age was above normal. This increase in comparison with normal children in the early stages seems to be reduced by acidosis and/or otherwise badly controlled diabetes.

An endocrine action on the growth of enchondral bone could not have been very common in diabetic children lacking acidosis since the skeletal age was normal in 64 per cent. The second form of growth of bone, the periosteal, could not be assessed roentgenologically. Quantitative determination requires comparative patho-anatomical examinations and no series were available for the purpose.

Summary

The skeletal age was assessed roentgenologically in 35 girls and 46 boys with diabetes mellitus, their ages ranging from 9 months to 15 years. Some acceleration was observed in 16 per cent, retardation in 20 per cent and normal conditions in 64 per cent. In the majority of the cases the retardation seemed to occur in connection with acidosis. In early childhood the retardation was perhaps due to some endocrinal factors following hepatomegaly. The cause of acceleration was not found, but the relationship between the acceleration and some well-known endocrinal circumstances in diabetic children of the same age is discussed. No definite relationship between the duration of the disease and the abnormal variations was revealed.

Le développement du squelette chez les enfants diabétiques.

L'état de développement du squelette a été déterminé radiographiquement chez 35 filles et 46 garçons atteints de diabète sucré, dont les âges chronologiques vont de 9 mois à 15 ans. On a observé un certain degré d'accélération dans 16 % des cas, du retard dans 20 % et un développement normal dans 64 %. Dans la majorité des cas le retard semble être en rapport avec l'acidose. Dans la première enfance le retard est peut-être dû à des facteurs endocriniens consécutifs à l'hépatomégalie. La cause de l'accélération n'a pas été trouvée, mais on discute la relation entre l'accélération et certains états endocriniens bien connus chez des enfants diabétiques du même âge. On n'a trouvé aucune relation bien déterminée entre la durée de la maladie et ces déviations.

Das Skelettalter bei diabetischen Kindern.

Das Skelettalter wurde bei 35 Mädchen und 46 Knaben mit Diabetes mellitus im Alter von 9 Monaten bis 15 Jahren röntgenologisch festgestellt. Etwas Akzeleration wurde in 16 % beobachtet, Retardation in 20 % und normale Verhältnisse in 64 %. In der Mehrzahl der Fälle schien die Verzögerung in Verbindung mit Azidose einzutreten. In der frühesten Kindheit beruhte die Retardation vielleicht auf gewissen endokrinen Faktoren infolge von Hepatomegalie. Die Ursache der Akzeleration konnte nicht festgestellt werden, aber der Zusammenhang zwischen der Beschleunigung und einigen wohlbekannten endokrinen Umständen bei diabetischen Kindern desselben Alters wird erörtert. Eine bestimmte Relation zwischen der Dauer der Krankheit und den Abweichungen war nicht zu konstatieren.

La edad ósea en los niños diabéticos.

La edad ósea por el estudio del desarrollo esquelético fué investigada radiológicamente en 35 niñas y 46 niños afectados de diabetes sacarina, cuyas edades estaban comprendidas entre 9 meses y 15 años. Un cierto grado de aceleración en el desarrollo óseo se observó en un 16 %, retraso en un 20 % y edad normal de desarrollo óseo en el 64 %. En la mayoría de los casos el retraso estaba en relación con la acidosis. En la primera infancia el retraso quizá era debido a algunos factores endocrinos subsiguientes a la hepatomegalia. La causa de la aceleración en el desarrollo óseo no pudo explicarse, pero se discuten las relaciones entre la aceleración del desarrollo esquelético y algunos factores endocrinos bien conocidos que concurren en niños diabéticos en esta edad. No se pudieron establecer relaciones definidas entre la duración de la enfermedad y el tipo de desviación observado.

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The Electroencephalogram in Enuresis

by

SIV GUNNARSON and K.-A. MELIN

By enuresis we mean repeated involuntary micturitions after the third year of life, mainly taking place during the night but, in some cases, in the daytime only. Statistics generally give the frequency of nocturnal enuresis as 18—25 per cent of all children (ADDIS, DESPERT). This shows that enuresis is a widespread symptom.

Much has been written concerning enuresis and its pathogenesis. Three main lines can be discerned in the discussion on this subject. Firstly, the *urologic* viewpoint which implies that, in many cases, an organic disturbance in the bladder or in the urethra causes the enuresis. Secondly, the *hereditary* viewpoint indicates an abnormality in the bladder function (BAKWIN) as the cause of the enuresis, i. e., a sensitive bladder which is easily influenced by psychic factors. Thirdly, the *psychiatric* viewpoint which explains the enuresis as a nervous symptom produced only by disorders of the personality.

In papers on enuresis, we have found that only one group is discussed, viz., children who are wet after the age of three years. Only a few authors divide enuretic children into two main groups (A. LICHTENSTEIN). One group comprises those always wet, and another those who had a dry period and then started to wet again. We consider this division into two groups rather an important one since, in practice in a department of child psychiatry, the prognosis of the treatment of these two groups differs. In the children who had a dry interval of one

year or more, a neurotic mechanism underlying the enuresis is in many cases traced. The simplest example of this is the child who is dry but starts to wet when a younger brother or sister is born. The psycho-genesis in the other cases may be much more complicated, though generally not impossible to ascertain. If the neuroses of the child in question can be successfully treated with psychotherapy, the enuresis is apt to be cured.

However, among those children who have never had a dry interval, there are some who do not show any neurotic traits, or only mild neurotic symptoms which may be the result of the enuresis, e.g., inadequate self-confidence etc., but which are not the actual cause of the trouble. The prognosis concerning the treatment of the enuresis of these children seems rather bad. All kinds of remedies are tried with only a brief effect, or none at all. Institutions dealing with play-therapy in children also report that play-therapy cures many neurotic symptoms but the continuous bed-wetting remains, as a rule, even after a successful psychotherapy.

In order to study the problems more closely, we started to use electroencephalography. The cases were first clinically examined, and those showing organic disturbances, such as pyelitis, oxyuriasis, diabetes mellitus or insipidus, etc., were excluded. 90 cases without organic lesions were examined by means of electroencephalography. Before stating the results, a few data regarding the psychiatric examination will be given. The 90 cases were divided into three different groups: the children with continuous enuresis totalled 64 cases, an intermediate group consisted of 9 children who had had a dry period of three to twelve months, and a third group contained 17 cases who had had a dry period of one to several years.

Among the 64 children always wet, 3 were slightly backward all the others in that group and in the two other groups being of normal intelligence. Heredity of enuresis was found twice as often among the children always wet as in the group with a long dry interval. As regards maladjustments, psychosomatic symptoms and milieu-injuries, no definite difference could be ascertained between the three groups. However, concerning the

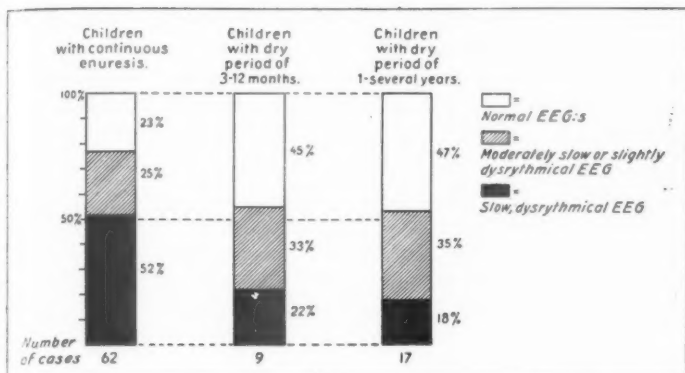
frequency of enuresis, a psychic influence was noted in 80 per cent of the children who had had a long dry period, while in only 18 per cent among the children always wet. Also among the latter, a larger number of infantile, immature children occurred than among those with a long dry interval (more than twice the number).

Since 1938, several papers have been published about the EEG findings in children with "behaviour disorders". The results have been discussed from many different points of view. There is undoubtedly a good correlation between the results published by the different investigators. They all agree that there is a high percentage of abnormality in the EEG:s of "behaviour-disorder-children" as compared to those of normal children. However, the problem is that the group of "behaviour disorders" is fairly heterogeneous. In the authors opinion the only way of approach is to divide this group into separate units and study each in turn.

Two years ago, we decided to attempt EEG examinations in order to study the children with enuresis from a new angle, and to try and find support for the theory concerning the different groups of enuresis. In the literature we could only find that some of the authors (MICHAELS, among others), writing on EEG in "behaviour problem children", had mentioned enuresis as a group of its own, without further discussion. In 1950, HELSBORG published a short study of enuretic children. However, he did not tackle the problem in the way we intended, but tried to find a hereditary connection with epilepsy, in particular.

In our investigation, one or two electroencephalograms were recorded with a Grass electroencephalograph, Model III. Colloidum-electrodes were used, 5 on each side of the head, and monopolar as well as bipolar leads were used in all the recordings.

Firstly, we stated that all the children with enuresis should be electroencephalographically examined in order to rule out epilepsy as a cause of the disease. We were convinced that only a few cases would reveal signs of epilepsy in the records, and recently we have found our suspicions justified. Two boys admitted to the hospital with a history of continuous enuresis, disclosed markedly pathological EEG's. One had a great many



spikes in the record. The other showed very short clinical petit mal attacks during the EEG registration, though earlier unobserved by the parents, and showed a typical "wave and spike" record. These were the only two patients among our 90 enuresis cases that showed epileptical discharges in the EEG.

The EEG's of the other 88 cases were classified in three groups, viz., normal, moderately slow or slightly dysrhythmic EEG's, and markedly slow or dysrhythmic EEG's. The abnormalities not infrequently consisted of a conspicuous component of 3—5/sec, large waves, very often localized to the occipital regions of the brain. Also various degrees of general dysrhythmia were found, sometimes combined with a more or less pronounced hypersynchrony. No lateralization or focal findings were observed in any single case.

Almost all the EEG's were read without any knowledge of the particular type of enuresis represented by the child.

When the EEG findings in the three groups are compared (Diagram I), we find a marked preponderance of markedly changed EEG's in the 'always wet' group. Only 23 per cent of the records could be classified as normal in this group, while in the group with a fairly long dry interval 43 per cent normal records were noted.

These findings, which will be more closely studied in a more

extensive series, fully support the viewpoint that in one group, viz., that of the children always wet, the enuresis seems to a great extent to be due to some form of brain change, most likely an immaturity. It is of interest to see that among 20 children in the 'always wet' group, who are described as infantile or immature in their emotional conduct, 15 show severe EEG disturbances, 2 slight ones and only 3 a normal EEG. The combined results of psychiatric and EEG investigations in these cases strongly support our theory of immaturity in the nervous system as the cause of enuresis in these children.

In these cases, which seem to be the most complicated ones, the treatment must be a combination of medical and psychological methods. In the other group, where brain changes are less marked, psychological factors seem to be the major factors of influence.

Summary

90 children with enuresis have been selected for an electroencephalographic study. They have been divided into two groups, viz., those who have had a dry period for one year or more, and those who have always been wet. There is, apparently, a marked difference between the EEG findings in these two groups, with a marked preponderance of pathological records in the 'never dry' group. This supports the theory of immaturity in the nervous system as the cause of enuresis in the always wet children. Attention is drawn to the fact, that two epileptics occurred among these children with enuresis.

L'électroencéphalogramme chez les énurésiques.

Quatre vingt dix enfants présentant une énurésie ont été choisis en vue de les soumettre à une étude électroencéphalographique. Ils furent divisés en deux groupes suivant qu'ils étaient toujours énurésiques ou ne l'étaient que depuis une période sèche d'une année ou plus. Il existe, en apparence, une différence marquée entre les tracés EEG de ces deux groupes. Celle-ci consiste en une nette prépondérance des altérations pathologiques chez les sujets qui persistaient dans leur énurésie. Ceci vient à l'appui de la théorie qui invoque l'absence de maturité du système nerveux comme cause de l'énurésie des enfants qui de sont encore souillés. L'attention est, de plus, attirée sur le fait que deux épileptiques faisaient partie de ce groupe d'enfants énurésiques.

Das Elektroencephalogramm bei Enuresis.

90 Kinder mit Enuresis wurden für eine elektroencephalographische Untersuchung ausgewählt. Sie wurden in zwei Gruppen eingeteilt: solche, die ein Jahr oder länger eine trockene Periode gehabt hatten, und solche, die immer genässt hatten. Es besteht augenscheinlich ein ausgeprägter Unterschied zwischen den EEG-Ergebnissen in diesen beiden Gruppen, mit einem ausgesprochenen Überwiegen pathologischer Befunde in der niemals trockenen Gruppe. Dies stützt die Theorie, dass Unreife des Nervensystems die Ursache der Enuresis bei den immer nässenden Kindern ist. Die Verfasser machen darauf aufmerksam, dass sich unter diesen Kindern mit Enuresis zwei Epileptiker befanden.

El electroencefalograma en la enuresis.

Noventa niños con enuresis fueron seleccionados para practicar en ellos un estudio electroencefalográfico. Se dividieron en dos grupos uno de los cuales comprendía niños que habían tenido un período seco durante un año o mas y otro en que durante este tiempo eran siempre enuréticos. Se comprobó marcadas diferencias entre los hallazgos del EEG en ambos grupos con un marcado predominio de registros patológicos en el grupo siempre seco. Ello apoyaría la teoría de inmadurez del sistema nervioso como causa de la enuresis en los niños siempre enuréticos. Se resalta el hecho de la existencia de dos epilepticos entre estos niños con enuresis.

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ACTH and Cortisone Treatment of Acute Rheumatic Fever

by

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Previous attempts to treat acute rheumatic fever with ACTH and Cortisone seem to have established the fact of a consequent rapid improvement in the general condition, as well as a disappearance of the articular symptoms and the temperature, and normalization of the sedimentation rate (1, 2, 3, 7, 8, 9, 12, 13, 14, 16, 19, 20).

Apparently, the carditis is also favorably affected by this treatment. Several cases are described, where murmurs, friction sounds, the cardiac enlargement and symptoms of decompensation disappeared and where the ECG changes reverted to normal. It is however difficult to evaluate this effect on the carditis, as these changes frequently occur spontaneously. Furthermore, the reported studies are as a rule comparatively small. Still, in several instances, the improvement was so rapid that it was, in all likelihood, attributable to the therapy. A recurrence of the cardiac symptoms has occasionally been noted after the treatment was terminated, in which case renewed therapy was successful in producing a second remission.

One of the principal aims in the treatment of acute rheumatic fever must be to prevent a more severe persistent valvular defect. Whether ACTH and Cortisone treatment have any effect in this respect is as yet impossible to decide. This can only be determined after several years' observation of a large number of cases.

In rheumatic fever the pathologic changes in the connective tissue have been tentatively related to disturbances in the hyaluronic acid-hyaluronidase-antihyaluronidase system. A significant increase in the antistreptococcal hyaluronidase has been demonstrated by HARRIS *et al.* (8) and others. The nonspecific anti-hyaluronidase factor occurs in increased titre in acute rheumatic fever in acute stages (5, 7), but also in a number of other conditions. The effect on this nonspecific antihyaluronidase factor of ACTH in rheumatic fever was studied by DOREMAN *et al.* (3) and by SCHMITH and FABER (17) and in rheumatoid arthritis by JONSSON *et al.* (10). As a rule a decrease in this serum inhibitor by ACTH has been ascertained.

ACTH and Cortisone have been suspected to exert an inhibiting effect on the antibody formation. However the results of clinical tests and animal experiments do not correspond (4, 6, 11, 15, 21).

Own investigations

Severe or fulminating cases of rheumatic fever have been uncommon in Stockholm during recent years. Generally the disease has had a benign character. Still the authors considered it worth while and justifiable to test the effect of ACTH and Cortisone also in these mild cases. At this time 7 cases aged 15 months to 13 years have been studied under the influence of these drugs. The ACTH-preparations employed were *Cortrophin* (Organon) and *Acton* (Fredriksbergs Chemical Manufacturers), the Cortisone-preparation was *Cortone* (Merck). The dosage of ACTH varied between 10 and 20 mg per day, and was divided into three intramuscular injections. Cortisone was applied in a dosage of 75—200 mg per day, in a few cases with decreasing dosage after a time, divided into 2—3 intramuscular doses.

Case Reports:

1. A girl aged 12 years. Fell ill on July 10th, 1950, with tonsillitis, which improved after a few days. On July 26th she again developed fever, associated with migrating articular symptoms, pain and swelling. She was treated for a month at a country hospital, during which time she was so severely ill as to have cardiac decompensation. She had

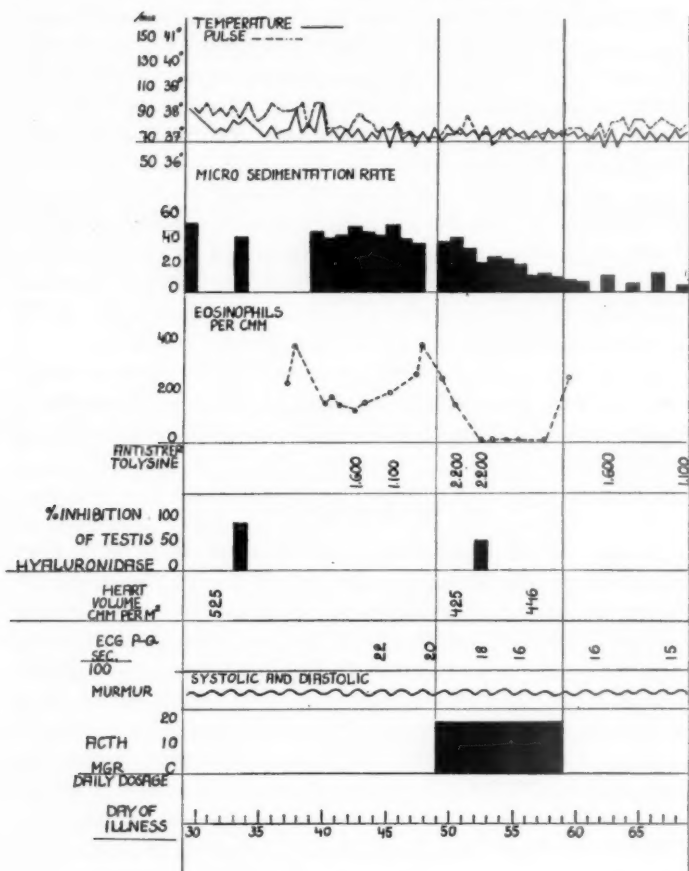


Fig. 1.

murmurs, friction sounds and the ECG disclosed a conduction time (P—Q) of 0.26. She improved, and after three weeks she was feverfree and had no joint symptoms. On admission to Norrtull's Hospital on Aug. 26th, she was still in bad general condition, thin, pale and too weak to sit up, but free from signs of cardiac decompensation. Cardiac examination disclosed a strong systolic and faint diastolic murmur over apex,

a prolonged P—Q (0.22) and a slight enlargement by roentgenography. Treatment with ACTH was initiated on Sept. 15th, (almost two month after the onset) 20 mg daily for 10 days. Within one or two days she began to show marked improvement, increasing appetite and cessation of weight-loss. The effect of the treatment in other respects is illustrated in Fig. 1. The sedimentation rate and ECG were rapidly normalized, and the heart volume diminished. During the treatment the antihyaluronidase effect of the serum fell from 85 to 66 (percentage inhibition in 0.075 cc of serum of $\frac{1}{2}$ V. R. U. bovine testicular hyaluronidase (*Hyalas*, Leo)). The physical heart findings nevertheless remained unchanged.

There was no recurrence of the symptoms following discontinuance of therapy.

2. A girl, aged 13 years, developed tonsillitis on July 18th, 1950. After a few days pain and swelling appeared in the joints of the feet, followed by migrating articular symptoms. Her temperature was 38°.5 to 39°.9 C. She was admitted to Norrtull's Hospital on July 24th. At that time she had pain in the neck joints, which subsided after a few days treatment with salicylates. Her general condition was good. Cardiac examination disclosed a harsh systolic murmur over the fourth left intercostal space, as well as a faint diastolic murmur. Radiography of the heart gave normal findings. ECG throughout was normal. There were no signs of decompensation. Hyaluronidase inhibition 50 per cent.

ACTH treatment was introduced on Aug. 11th and she was given 15 mg of ACTH daily for 7 days. As is shown in Fig. 2, the sedimentation rate was normalized. The murmur changed, leaving only a soft systolic murmur. Hyaluronidase inhibition fell at first to 32 per cent and after treatment was discontinued to 17.

There was no relapse following cessation of treatment.

3. A girl, aged 15 months, became acutely ill on Nov. 14th, 1950, with fever and signs of a common cold. On standing she seemed to have pains in her joints. She was treated with sulfa and penicillin at home, but the temperature continued to run 39°—40° C. She was admitted to an Epidemic Hospital on Dec. 2nd with a suspicion of poliomyelitis. Aside from the fever, there were no noteworthy findings, the cerebrospinal fluid was normal. Penicillin treatment was continued, but the irregular fever persisted, and she showed a marked deterioration. On Dec. 7th she was transferred to Norrtull's Hospital. Examination at this time showed: Marked pallor, but no cyanosis, dyspnoea or edema. The following day she had a constant rough pericardial friction sound. Blood cultures and serologic studies were normal. Roentgenographic studies showed some cardiac enlargement but no evidence of pericardial fluid and no significant pulmonary changes. The ECG was normal.

Since the diagnosis of rheumatic pericarditis was uncertain, she was

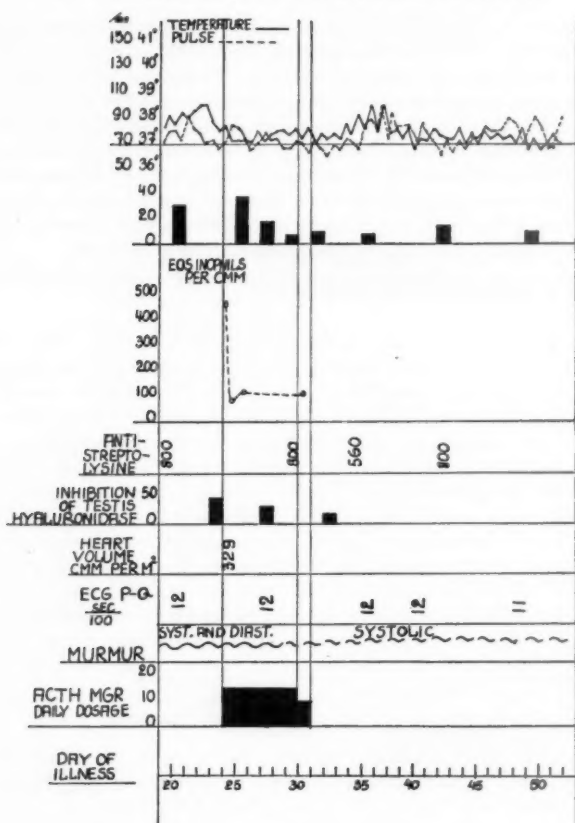


Fig. 2.

first treated without effect with aureomycin and then with terramycin for a possible bacterial infection.

Treatment with ACTH was initiated and within four days an improvement was apparent. Although this improvement took place twelve hours after the terramycin had been administered, the course shows that the effect must be attributed to the ACTH therapy. For, when the ACTH dose was decreased from 10 to 5 mg daily, a relapse occurred that failed to respond to renewed terramycin treatment, but was favorably affected by an increase in the ACTH dose to 10 mg. The course and

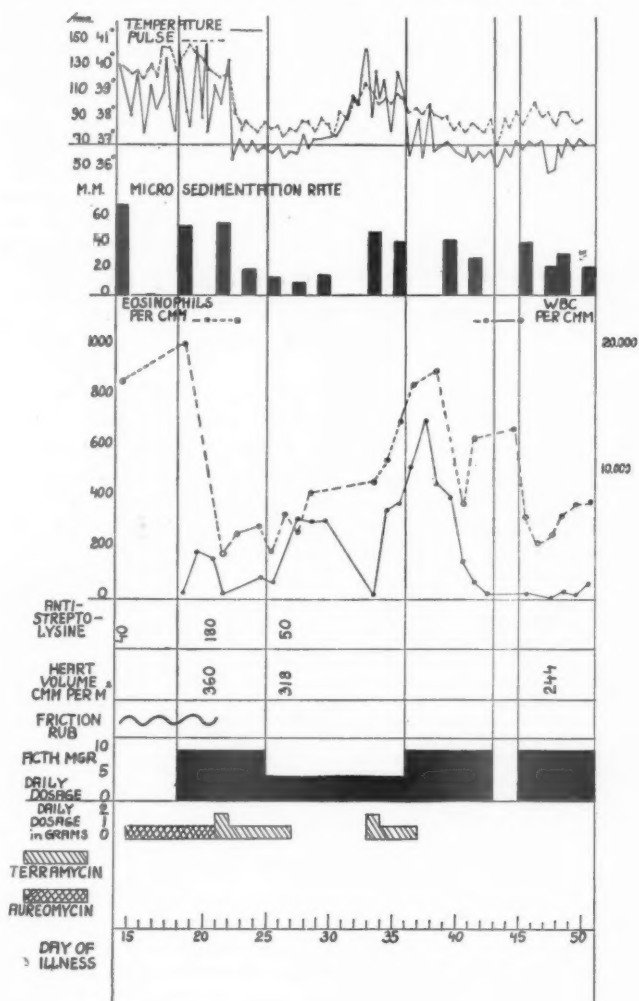


Fig. 3.

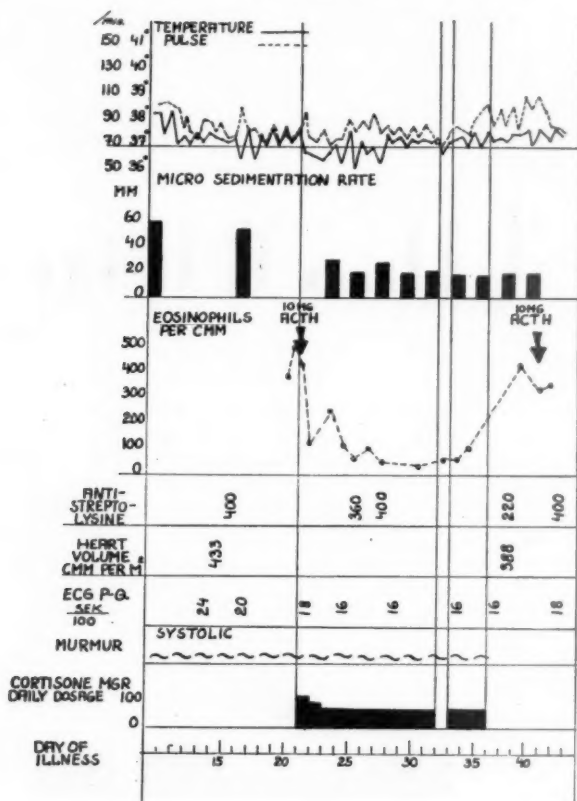


Fig. 4.

effect of the treatment is illustrated in Fig. 3. During ACTH treatment the general condition improved. Where she had previously been sluggish and tired, had refused to eat, lying apathetically in bed, she now became livelier, had a good appetite, began to gain weight and took an interest in her surroundings. Her temperature and sedimentation rate rapidly became normal. The friction sounds disappeared. She was discharged 14 days after cessation of therapy on Feb. 1st, 1951 quite free from symptoms.

In March, 1951 she again developed fever, swollen ankle joints, and

a high sedimentation rate, but no cardiac symptoms or findings. Renewed ACTH treatment was administered and is still in progress. She does not seem to react so well this time.

4. Boy, aged 8 years, became ill with tonsillitis about Oct. 15th, 1950. On Nov. 10th, he began to have articular symptoms and a slight fever (max. 38° 5 C). When admitted to Norrtull's Hospital on Nov. 20th he had swelling and pain in the knee joints. These articular symptoms however subsided after two days. Cardiac examination revealed an apical systolic murmur, a prolongation of the P—Q (0.24) and slight cardiac enlargement by radiography.

Cortisone treatment was initiated on Dec. 3rd, but normalization of the sedimentation rate and ECG had already started. The Cortisone dose was 100 mg on the first day, followed by 75 mg daily for 10 days. His clinical course is shown in Fig. 4. After the therapy the murmur disappeared.

Before the Cortisone treatment he was given a test dose of ACTH and a marked decrease in the number of circulating eosinophile leukocytes occurred, but after the treatment this effect did not occur.

5. A boy, aged 12 years, developed an otitis late in Sept. 1950, which was treated with penicillin. On Oct. 13th, he again became ill with a fever of 40° 0 C and chills. He was then confined to bed with a remittent temperature, until admission to Norrtull's Hospital on Oct. 23rd. Cardiac examination revealed an apical systolic murmur, a radiographically normal heart, a slightly prolonged conduction time (0.18), and depressed S—T segments in leads 2 and 3. Hyaluronidase inhibition was 85 per cent.

Cortisone treatment was initiated on Oct. 30th, and he received 75 mg daily for 11 days. He was afebrile before treatment was started, but during treatment the murmur disappeared, the ECG became normalized and the sedimentation rate decreased. Hyaluronidase inhibition was slightly reduced. About a week after treatment, the sedimentation rate increased somewhat in connection with a sinusitis, but there was no recurrence of the cardiac symptoms. His course is illustrated in figure 5.

6. A boy, aged 10 years, developed fever and a pain in his back, followed on succeeding days by moderate migrating articular symptoms and a fever of 38°—40° C. On admission to the hospital, he was apparently well except for slight swelling and tenderness in both ankle joints. Heart: A harsh systolic murmur over third left intercostal space, and a short, ringing diastolic murmur were present. The conduction time was 0.20. The heart was normal radiologically. The ESR was 55 mm. The hyaluronidase inhibition was 64 per cent. During a week of observation at the hospital, the fever and articular symptoms subsided, but the ESR remained high, and the physical heart changes remained unchanged, though the P—Q time decreased from 0.20 to 0.17.

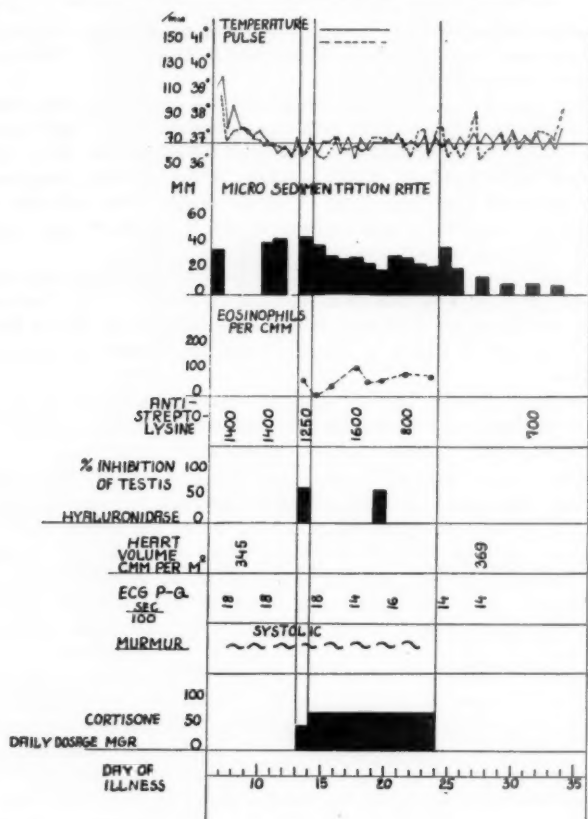


Fig. 5.

Cortisone was introduced on the twelfth day of illness in a dosage of 200 mg, on the following day 150 mg, and then for 9 days 100 mg, after which time the drug was gradually withdrawn in the course of 5 days. The effect of this therapy is illustrated in Fig. 6. The ESR became normal after 11 days of treatment, the diastolic murmur was inaudible and the systolic murmur had lost its harshness. The P—Q time was reduced to normal values. The heart volume was unchanged. The hyaluronidase inhibition diminished to 4 per cent after 5 days.

After cessation of treatment the eosinophile leukocytes failed to

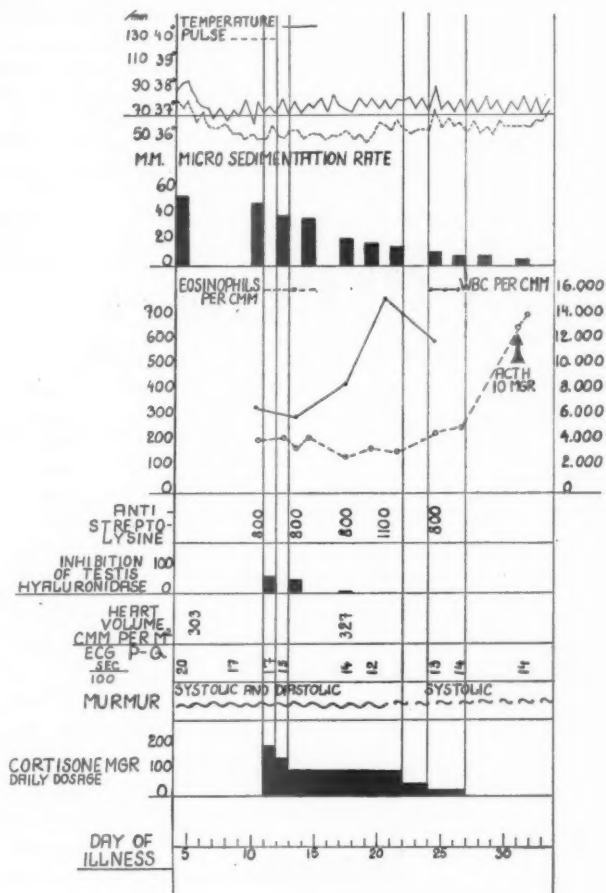


Fig. 6.

respond to a single dose of ACTH. There was no recurrence of the symptoms.

7. A boy, aged 13 years, developed a sore throat on Jan. 11th, 1951. He had a high fever for five days. After a few days of freedom from fever there was a recurrence of the fever with moderate pain in the knee and ankle joints. On admission to the Hospital on Jan. 25th, he was

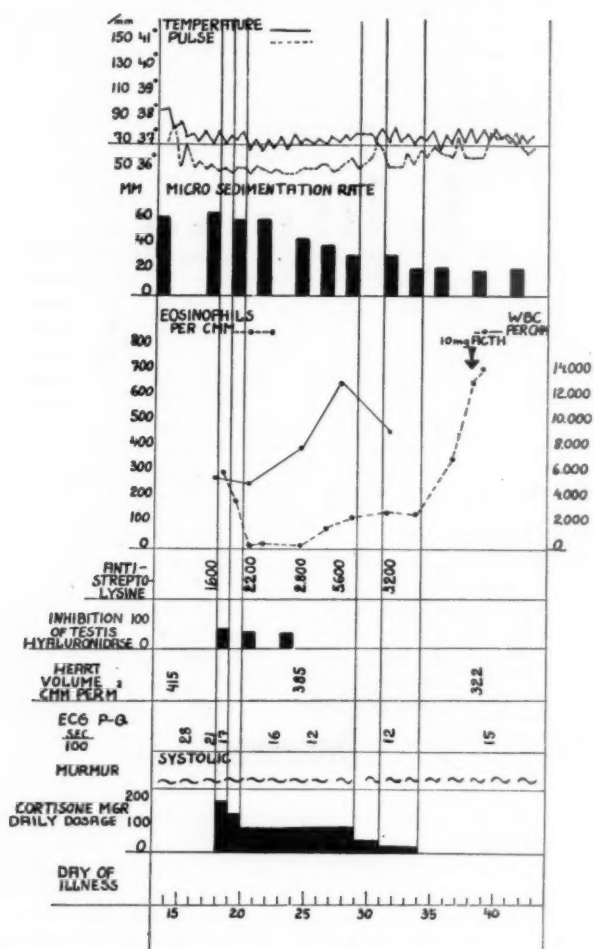


Fig. 7.

tired, had a greyish palor and was slightly dyspnoic. The knees and feet were swollen and tender with reduced mobility. Cardiac examination showed a soft systolic murmur maximal in the fourth left intercostal space, a prolonged P—Q (0.28), radiologically an enlargement to a volume of 415 cc per m² of body surface and slightly prominent pulm. A. region. While under observation the ESR remained high, the murmur became louder and harsher, and the P—Q time diminished to 0.21.

Cortisone was introduced 19 days after the initial tonsillitis at a dosage of 200 mg, on the following day 150 mg and then 100 mg for 9 days, after which time the drug was gradually withdrawn in the course of 5 days, as is shown in Fig. 7. During the therapy the ESR fell to 20 mm. After 11 days' treatment, though still harsh in character, the murmur became less marked and was only faint at the termination of the treatment. The heart volume decreased to normal values. The hyaluronidase inhibition decreased.

After the withdrawal of the drug, he was observed in the hospital for 3 weeks without evidence of relapse. The eosinophiles did not decrease after a single dose of ACTH in the post treatment period.

Discussion

While most of our cases were very mild without fever or arthritis when the treatment was begun, and so do not permit evaluation of the effect of treatment on this symptoms, case 3, who was admitted in an acute stage, seriously ill, with a high fever became rapidly afebrile and markedly improved in her general condition.

All the patients showed a rapid decrease in the sedimentation rate to normal levels. The antistreptolysin titres did not seem to have been affected. The titres were in several instances already falling when the therapy was initiated and no influence on the reduction took place in connection with treatment.

In 5 cases a nonspecific antihyaluronidase factor was examined. In every instance there was, during the ACTH and Cortisone treatment, a falling titre of varying magnitude.

The effect of therapy on the carditis is even more difficult to evaluate. In all of the 5 cases which had at the onset pathologically abnormal ECG, the changes rapidly disappeared under treatment, but some of them had shown some improvement prior to the treatment. Case 3 initially showed a normal ECG,

but after a few days of ACTH treatment T_1 became isoelectric, only to become normal again after another few days. The same transient change occurred also later in the course in connection with an increase in the dosage, following a partial withdrawal. These changes were probably due to a temporary electrolytic disturbance with increased excretion of potassium. ACTH therapy involves an early transient fluid retention, which may further aggravate a severe cardiac decompensation. This secondary effect was not observed in these patients, who were in a stage of good compensation during the treatment.

Murmurs and friction sounds disappeared or were markedly improved in character in all the cases but one, case 1, where however the treatment was not introduced until two months after the onset of the disease. The fact that murmurs in the acute stage disappeared in connection with the treatment cannot be taken as proof that endocarditic changes had healed. These murmurs in some instances are probably due to cardiac dilatation, secondary to myocardial injury, and they therefore disappear early in the course of the disease, when the dilatation has receded. A decrease in the heart volume radiologically was observed in two cases. Relapse after treatment occurred in only one case, and only after a period of over one month of freedom from symptoms.

There are no definite principles for the determination of the dosage of ACTH in children. It is uncertain whether the dose in children can be reduced proportionally with the body weight or body surface. The degree of severity of the disease might be more decisive. It has been contended that the effect on the eosinophile leukocytes best denotes the adequacy of the dosage. The three cases given ACTH responded with a pronounced decrease in the eosinophiles. Case 3, however, had a more noteworthy reaction. She was in very poor general condition at the beginning of the therapy, and, as is often the case in such states, the number of eosinophiles was very low and remained low throughout the period when she was receiving 10 mg of ACTH. When the dose was reduced to 5 mg, the eosinophiles began to increase and this was assumed to indicate that this dose was too

small. The later clinical course served to confirm this. When the dose was again raised to 10 mg the eosinophiles decreased.

THORN and his coworkers demonstrated that no decrease takes place in the number of eosinophiles after a single dose of ACTH during or just after Cortisone treatment. It has been assumed that the Cortisone treatment reduces the function of the adrenal cortex through an inhibition of the ACTH-production of the pituitary gland. The adrenals would then fail to respond to a single dose of ACTH. In cases 4, 6 and 7 the decrease in the number of circulating eosinophile leukocytes after 10 mg of ACTH did not occur when the Cortisone treatment was discontinued. It might be advisable to discontinue Cortisone treatment slowly by successively decreasing the dosage.

Concerning the late prognosis in our cases it is impossible to predict the frequency of permanent endocardial changes of clinical importance. It is still more impossible with this short time of observation to evaluate, if ACTH and Cortisone have had any inhibiting properties in this respect.

Conclusion and Summary

1. Three cases of rheumatic fever were treated with ACTH and four cases with Cortisone. All cases showed signs of cardiac involvement.

2. During treatment the ESR rapidly fell to normal. Heart murmurs and pericardial friction sounds decreased or disappeared in all but one case, where the treatment was started late in the course of the illness. ECG-changes being present in six cases disappeared. In one case symptoms reappeared one month after treatment.

3. In one case treated with ACTH ECG-changes, apparently caused by potassium deficit, occurred. No other side reactions were observed.

4. The adequate dosage of ACTH and Cortisone in treatment of children with rheumatic fever is at present not definitely established. For treatment with ACTH the decrease in the number of eosinophile leukocytes seems to be a valuable guide.

5. At the present stage it is impossible to decide whether treatment with ACTH or Cortisone can prevent damage to the heart. Observation of a larger number of patients for several years will be necessary before this important question can be answered.

Traitement du rhumatisme articulaire aigue par l'ACTH et la Cortisone.

1. Trois cas de R. A. A. ont été traités à l'ACTH, et quatre cas à la Cortisone. Dans tous ces cas, il y avait une atteinte cardiaque.

2. Pendant le traitement, la V. S. est tombée rapidement à la normale. Les souffles cardiaques et les frottements péricardique diminuèrent ou disparurent dans tous les cas sauf dans un seul où le traitement avait été commencé tardivement. Les alterations électrocardiographiques présentes dans 6 cas, disparurent. Dans un cas, des symptômes pathologiques réapparurent un mois après la fin du traitement.

3. Dans un de cas traités à l'ACTH, on a noté des alterations de l'Ecg, vraisemblablement secondaires à une hypokaliémie. On n'a observé aucune autre manifestation.

4. La posologie exacte de l'ACTH et de la Cortisone dans le traitement du R. A. A. de l'enfant n'est pas encore définitivement fixée. Pour le traitement à l'ACTH, la chute de l'éosinophilie sanguine semble être un guide valable.

5. A l'heure actuelle, il est impossible de savoir si un traitement à l'ACTH ou à la Cortisone peut prévenir une lésion cardiaque. Il sera nécessaire de suivre un grand nombre de malades pendant plusieurs années avant de pouvoir donner une réponse à cette importante question.

Behandlung des akuten rheumatischen Fiebers mit ACTH und Cortison.

1. Drei Fälle von rheumatischem Fieber wurden mit ACTH und vier Fälle mit Cortison behandelt. Alle Fälle wiesen Anzeichen von Herzprozessen auf.

2. Während der Behandlung kehrte das ESR rasch zur Norm zurück. Herzgeräusche und pericardiale Reibegeräusche nahmen ab oder verschwanden in allen Fällen bis auf einen, wo mit der Behandlung spät im Verlaufe der Krankheit eingesetzt wurde. Die in sechs Fällen vorhandenen ECG-Veränderungen verschwanden. In einem Fall kehrten die Symptome 1 Monat nach der Behandlung zurück.

3. In einem mit ACTH behandelten Fall kamen ECG-Veränderungen vor, wahrscheinlich durch Kaliummangel verursacht. Es wurden keine Nebenwirkungen beobachtet.

4. Die entsprechende Dosierung von ACTH und Cortison in der Behandlung von Kindern mit rheumatischem Fieber ist zur Zeit nicht endgültig festgestellt. Bei der Behandlung mit ACTH scheint die Abnahme der Anzahl von eosinophilen Leukozyten ein wichtiger Leitfaden zu sein.

5. Im jetzigen Stadium ist es unmöglich zu bestimmen, ob die Behandlung mit ACTH oder Cortison eine Dauerschädigung des Herzens

verhindern kann. Bevor diese wichtige Frage beantwortet werden kann, wird die Beobachtung einer grösseren Anzahl von Patienten mehrere Jahre hindurch notwendig sein.

Tratamiento de la fiebre reumática aguda con ACTH y cortisona.

1. Tres casos de fiebre reumática fueron tratados con ACTH y cuatro con cortisona. Todos ellos mostraban signos de participación cardíaca.

2. Durante el tratamiento la velocidad de sedimentación globular se normalizó rápidamente, los soplos cardíacos y los ruidos pericárdicos disminuyeron o desaparecieron en todos los casos. Las alteraciones electrocardiográficas presentes en 6 casos desaparecieron. En uno de los enfermos reaparecieron los síntomas un mes después del tratamiento.

3. En uno de los casos tratados con ACTH aparecieron alteraciones del trazado electrocardiográfico aparentemente debidas a un déficit de potasio. No se observó ninguna otra reacción.

4. Actualmente no está establecido todavía de un modo definitivo el criterio de dosificación del ACTH y cortisona en el tratamiento de la fiebre reumática. Para el tratamiento con ACTH el descenso del número de eosinófilos parece ser una valiosa guía.

5. En el estado actual de los conocimientos es imposible decidir si el tratamiento con ACTH o cortisona puede prevenir la aparición de una lesión cardíaca. Es necesaria la observación de un gran número de pacientes durante varios años antes de que pueda responderse a esta importante cuestión.

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Intravenous Iron Therapy in Pediatrics

by

BENGT HAGBERG

Searches have been made for a very long time for compounds of iron suitable for intravenous injection. The earlier preparations which we know of have more disadvantages than advantages. Ordinary, easily dissociable salt solutions of the type of ferro ammonium citrate, ferro ascorbate or ferri hydroxide give unpleasant toxic symptoms even in doses of about 10 mg Fe in adults, i. e., in amounts that are of little use therapeutically. GOETSCH, MOORE and MINNICH (1946) made experiments by giving colloidal ferri hydroxide in single massive doses which at times exceeded 1000 mg Fe. Its use, however, involved such severe side reactions that the authors concluded that "parenteral administration of iron is impracticable, dangerous and unnecessary as a therapeutic procedure."

In 1947, however, NISSIM reported good results in hypochromic anemia with another iron compound complex, a saccharated oxide of iron, which was tolerated remarkably well even in massive single doses. This iron compound, in improved variations, has since been found to fulfill the requirements necessary for an injectable iron preparation better than all hitherto used. A good series of cases treated has now been published (1, 2, 3, 7, 10, 11, 14, 15, 16, 22, 24, 28). It would seem, however, that this form of therapy has been very little used in children. At all events one only comes across a few reports about this in the literature. Nevertheless, DICKSTEIN and others (1951) give a report concerning a large material comprising 80 children between the

ages of 2 months and 6 years suffering from iron deficiency anemia of a primary nutritive genesis. As a rule the hematologic responses were quick and good. The final hemoglobin level was usually determined within three weeks, and it averaged 12.2 g %. Slight toxic reactions were observed in only 3 out of 199 injections, despite the fact that the amount of iron per kg body weight seems to have been rather considerable.

In this paper, the author would like 1. to give an idea about the behaviour of saccharated oxide of iron in the blood, 2. to give an account of his clinical experiences in treating 21 children of whom the majority were suffering from anemia of iron deficiency type, and 3. to establish indications for the use of intravenous iron therapy in children.

1. The behaviour of saccharated oxide of iron in the blood

One cannot help wondering how it is that saccharated oxide of iron, which at times gives very high iron concentrations in serum, is for the most part so well tolerated. Experiences gained in recent years in connection with the way in which iron passes through the blood give valuable information on the matter (19). Iron that is not hemoglobin-bound, i. e. serum iron, with its normal value of approximately 100 γ -%, occurs bound to a special β_1 -globulin, the transferrin or siderophillin, in a firm iron-protein complex. The total iron-binding capacity of normal serum amounts to 300—400 γ -%. Thus, only one third of the globulin fraction is used for iron-binding in ordinary cases. If one then injects an easily dissociable iron solution into the blood, the whole fraction is rapidly saturated with iron. According to the degree in which the capacity is exceeded and the surplus iron extravasated one gets the usual symptoms of iron intoxication (19). If, on the other hand, one injects saccharated oxide of iron, this appears initially in the blood in an unchanged form and a high concentration; besides there is partial saturation of the iron-binding globulin. Gradually, increasing amounts of soluble iron that can be added to this protein fraction are liberated (Fig. 1). The mechanism for the transformation of iron from

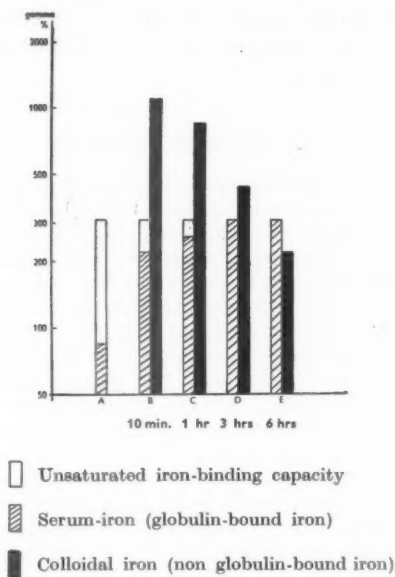


Fig. 1. The unsaturated iron-binding capacity and the iron content of serum before (A), and after intravenous injection of 100 mg Fe in 5 ml Intrafer (B—E). Note that the iron in saccharated iron preparations is not quantitatively regained with the ordinary serum-iron technique (30). (The values are for a 22 year old nurse with a slight hypochromic anemia. She displayed no toxic reactions after the injection of Intrafer.)

a colloidal to an easy dissociable form is not quite clear. According to CAPPEL (1930) and ANDERSSON (1950) in experiments on mice and rabbits respectively, saccharated oxide of iron injected intravenously is taken up by reticulo-endothelial cells in the same way as suspensoid substances, e. g. carbon. In the reticulo-endothelial cells the iron is converted from a finely particulated to a soluble form and is redistributed to the depots, mainly the parenchymal cells of the liver. This process seems to be rather slow, taking days to weeks. It is the present author's opinion that, in addition, there may also be a breaking down of saccharated iron directly in the blood, perhaps due to an enzymatic

activity. Increasing saturation of the iron-binding capacity during the first few hours after the injection, speaks in favour of this theory (Fig. 1).

2. Therapeutic experiences

Material: The 21 cases treated (see Table 1) comprised 12 cases of iron deficiency anemia, one hemorrhagic anemia that had just recovered from a bout of rheumatic fever, four postinfectious anemic conditions of a slight nature, two cases of ulcerative colitis, one current nephritis, one case of lupus erythematosus disseminatus with a constant feverish temperature, and lastly one case who refused to take food and who could not be persuaded to take iron per os. There were several types of iron deficiency anemias: a 12 year-old girl with a hereditary form; two cases of celiac disease, of which one was grave with a previous stubbornly resistant hypochromic anemia of many years standing; one case of ulcerative colitis that was in the process of healing and with secondary iron deficiency; three children of one year of age of the gruel-eating type with simple, nutritive iron deficiency; two other one year-old infants with hypochromic anemia following a prolonged condition of post infectious anorexia; and finally three idiots whose iron deficiency was of a mixed, though primarily nutritive nature.

The diagnosis of iron deficiency anemia was based on a decreased colour index, a low serum iron, and a raised iron-binding capacity in serum (the normal values in children are lacking for the time being but these, in view of the author's experiences, coincided to a large extent with those of adults). At least two, and in most cases all three criteria were manifest. Increase of the iron-binding capacity seemed to be consistent and most certain. This increase has been considered as being the more or less fruitless efforts of the organism to mobilize iron from the depots for the production of hemoglobin. An increase, then, of the unsaturated as compared with the saturated iron-binding globulin fraction is supposed to promote a greater flow of iron from the depots to the blood stream (19).

Methods: A spectrophotometric method in accordance with RATH-FINCH (1949) was used in order to determine the unsaturated iron-binding capacity of the serum. The principle is based on the fact that a progressive development of red colour occurs on the addition of iron

to the β_1 -globulin until the protein becomes saturated. The serum iron was determined in accordance with VAHLQUIST's method (1941) with minor modifications. The hemoglobin was measured with an *Autenrieth* hemoglobinometer. The usual clinical methods were used for examining the erythrocytes and reticulocytes.

Preparation, calculation and dosage: Various preparations of saccharated oxide of iron have appeared on the market. The author consistently used *Pharmacia's* "Intrafer"¹ which is identical in manufacture with a preparation used chiefly in England called "Ferrivenin" marketed by BENDER. Each ampule of "Intrafer" contains 5 ml 2% saccharated oxide of iron corresponding to 100 mg molecular iron. The total amount required for each individual case can be conveniently calculated in accordance with the following formula: kg body wt. \times Hb. deficiency in g% \times 2.5 = mg Fe, where 2.5 is the blood volume factor. No regard, however, has been paid in the above formula to the impoverishment of iron deposits which usually must be taken into account with hypochromic anemia. In the following material the calculation therefore was estimated higher, namely:

$$\text{kg body wt.} \times (15 - \text{Hb. in g\%}) \times 2.5 = \text{mg Fe}$$

The method of administration for children originally suggested and which consisted of repeated doses (20 + 20 + 60 . . mg Fe) is difficult to carry out in practice in those ages most profusely represented in a series of pediatric iron deficiency anemias, namely those between one and two years. For this group especially, and even for somewhat older children, it is desirable that the number of injections should be reduced to the least possible, both for technical and psychological reasons. The author therefore tried to administer the preparation in the form of single massive doses which naturally would be the ideal method of administration.

Technique: The technical details in regard to the injections are of special interest to pediatricians. Amongst other things it is often impossible to keep to the slow rate of injection recommended. The author thinks, from his own experience, that this is of no significance. Despite the fact that, almost consistently, the injections were given rapidly to infants, it was only in one case that any direct outside symptoms were observed, and even these were very slight. The same thing applying to the speed of the injection applied to the recommended buffering with aspirated blood in the syringe. Further, it is stated that fewer side issues occur if glass syringes are used. As such syringes were used consistently, no opinion concerning the relevancy of this statement can be

¹ The iron preparation used was kindly supplied by Pharmacia Ltd., Manufacturing Chemists in Uppsala, Sweden.

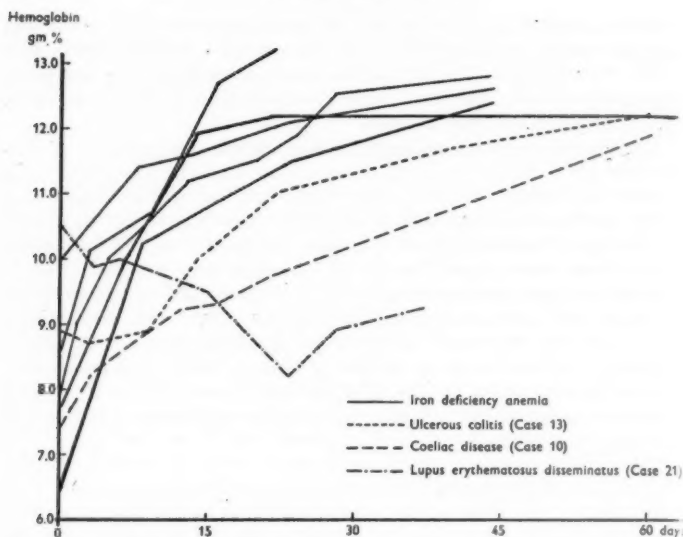


Fig. 2. Hemoglobin responses following intravenous iron therapy with saccharated oxide of iron (Intrafer).

given. On the other hand, the use of two different syringes, one for venipuncture and one for injection, can be recommended, as the brown-black, opaque colloid renders it difficult to verify the position of the puncture needle. It is true that the risks attending paravenous injections seem to be comparatively small, especially if the injection is made into a cubital vein, and yet one occasionally sees a necrosis such as, on one occasion, occurred on the dorsum of the foot.

Results and discussion: The results of treatment were consistently good in afebrile patients without current infection. In these the given dose entailed the estimated increase of hemoglobin (see Fig. 2). The majority reacted promptly with a surprisingly rapid increase of hemoglobin (cases 1, 2, 3, 5, 6, 7, 8, 9, 11 and 12). During the first two weeks there was an average daily increase of 0.25 g% in these cases. In differentiating from this type of hemoglobin response, one found in cases 4, 10 and 13 a slower remission curve which, after the first week, stayed

at an unchanged, or very slightly raised level. Decreased plasma protein values have been supposed to be one possible cause of the slow responses (24). This occurred in case 10, a boy with celiac disease, described in detail below. He had plasma protein values of about 6 g%. The maximum hemoglobin value, however, was nearly the same as that of the first group. On the whole, sideropenic children attained a hemoglobin value of 12.5 g% (12.2—13.7), which corresponds to a fully satisfactory normal value. The same high maximum hemoglobin value was obtained even in the remaining mixed cases, except for the last case, an 11 year-old girl with grave lupus erythematosus disseminatus and fever of a continuous type. Despite the fact that large doses of iron were administered repeatedly she showed a reduction rather than an increase of both hemoglobin and serum iron. With regard to the others, who all responded well, one must not forget that the spontaneous hemoglobin remission capacity is great after both infection and hemorrhage. For this reason there is no justification for any quantitative estimations in these mixed cases. Besides this, the infections in many of the cases were already totally or partially abated when iron was given. One detail which is not manifest in Fig. 2 is the slight initial decrease (0.3—0.7 g%) in hemoglobin values which was usually seen on the day following injection and which is possibly due to hemodilution (24, 17).

The changes in the red blood cell picture were insignificant in comparison with the marked increase of hemoglobin. Despite this, however, a rather typical reticulocyte crisis was observed in some of the cases. Such significant summits as have been registered in adults, 200 per thousand and over, have not been observed. As a rule one saw the maximum on the 3rd to the 7th day. Characteristically enough, there was no manifestation of any reticulocyte summit in two of the cases that had a slow hemoglobin remission, until very much later, namely on the 19th day in case No. 10, and on the 14th day in case No. 13.

An increase of the serum iron to normal values could be observed in the children with good hemoglobin remissions. The initial effect on the total iron content of the plasma was marked.

Case no. sex age, yrs	Diagnosis	Before Treatment			
		γ % SI	γ % TIBC	Colour index	g % Hb
1. ♂ 1½	Iron Deficiency Anemia	40	490	0.77	7
2. ♂ 1	Iron Deficiency Anemia	54	534	0.60	7
3. ♂ 1	Iron Deficiency Anemia	46	493	1.00	14
4. ♀ 1	Iron Deficiency Anemia	72	452	0.72	10
5. ♀ 1	Iron Deficiency and Megaloblastic Anemia	64	501	0.65	9
6. ♀ 12	Iron Deficiency Anemia (essential hereditary)	31	531	0.48	6.1
7. ♂ 5	Iron Deficiency Anemia + Idiocy ..	78	518	0.74	7.5
8. ♂ 6	Iron Deficiency Anemia + Idiocy ..	80	515	0.73	10.0
9. ♂ 1	Iron Deficiency Anemia + Idiocy ..	40	490	0.83	8.6
10. ♂ 8	Celiac Disease + Iron Deficiency Anemia	62	—	0.69	7.9
11. ♂ 2	Celiac Disease + Iron Deficiency Anemia	28	478	0.84	10.0
12. ♀ 1	Ulcerative Colitis + Iron Deficiency Anemia	76	561	0.80	10.5
13. ♀ 5	Ulcerative Colitis + Iron Deficiency Anemia	54	379	0.85	8.9
14. ♀ 8	Anemia Sec. (Blood Loss)	22	302	1.03	9.2
15. ♀ 10	Anemia of Infection (Status post febr. rheum.)	96	276	0.92	10.2
16. ♀ 2	Anemia of Infection (Status post Bronchit.)	98	328	0.93	10.5
17. ♂ 5½	Anemia of Infection (Lymfadenitis colli sanans)	36	251	1.00	10.5
18. ♂ 4	Anemia of Infection (Status post pneumon.)	52	287	1.00	10.9
19. ♂ 5	Nephritis + Anemia	88	438	1.00	10.7
20. ♀ 3½	Anorexia	160	345	0.95	11.0
21. ♀ 11	Disseminated Lupus Erythematosus	104	339	1.00	10.5

SI = Serum Iron.

TIBC = Total iron-binding capacity of serum.

After Treatment					mg Fe (Intrafer)			Number of injection
1 w. g % Hb	2 w. g % Hb	3-4 w. g % Hb	2 mths g % Hb	Max. Retic. ¹ / ₁₀₀	Calcu- lated need	Injec- ted	Single doses per kg	
15.0	11.9	12.1	12.2	—	180	100	10	1
11.1	—	12.0	10.5	60 (2) ¹	150	110	11	1
11.9	11.7	12.2	—	—	110	50	5	1
10.3	—	11.9	12.0	—	100	90	11	1
10.5	11.2	12.5	13.0	62 (3)	160	180	11	2
8.3	—	10.4	²	88 (5)	800	500	7	3
10.2	—	11.5	12.4	—	375	300	15	1
11.4	—	12.1	12.6	—	225	220	11	1
10.7	12.7	13.2	mors	95 (4)	120	250	17	3
8.9	9.2	9.7	11.7	130 (10)	350	200	10	1
11.7	11.7	12.2	10.7	54 (3)	150	100	9	1
12.7	—	13.7	—	23 (4)	120	90	10	1
8.9	10.0	11.0	12.2	58 (14)	260	200	6	2
—	11.0	12.5	12.7	—	400	200	3.5	2
11.5	12.1	12.7	12.0	28 (7)	300	300	4	3
12.0	11.4	—	12.3	23 (6)	100	50	6	1
12.6	12.6	—	—	37 (7)	250	250	13	1
12.7	12.0	13.5	—	—	115	150	9	1
11.2	11.7	12.3	12.5	—	225	100	5	1
12.2	12.2	—	—	11 (4)	60	60	5	1
10.0	9.5	8.8	8.2	35 (4)	315	400	7	3

¹ = Day for the maximal reticulocyte count.

² = Peroral iron therapy added.

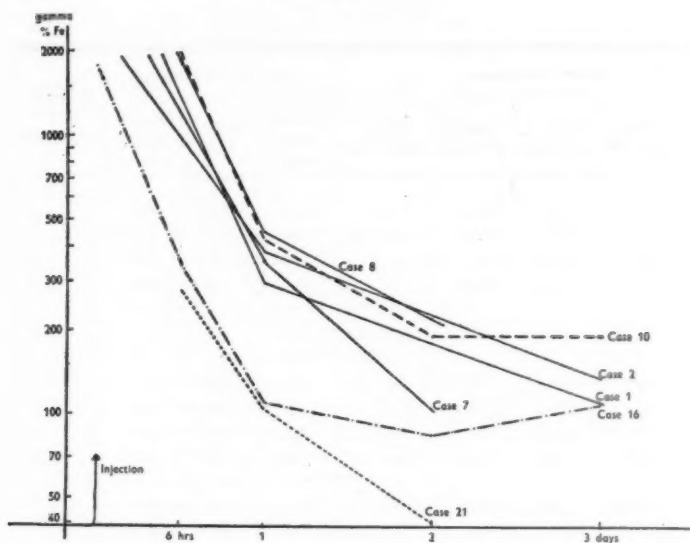


Fig. 3. The immediate effect of i. v. saccharated oxide of iron on the iron content in serum.

Immediately after the injection (i. e. 10 minutes), iron concentrations of up to 6000 $\gamma\%$ were measured (case 2). And even after a lapse of 6 hours the concentrations were, as a rule, still high, about 1000 $\gamma\%$. After one day they fell to between 200 and 400 $\gamma\%$ (see Fig. 3). The iron-binding capacity was continuously followed in one single case that remained for a long time in hospital. As will be seen from table 2, case No. 11 (celiac disease) manifested a definite reduction during the month following the treatment. Despite a satisfactory hemoglobin value and a normal serum iron, the iron-binding capacity, however, did not fall below 400 $\gamma\%$, probably emphasizing a latent deposit deficiency of iron. From table 1 it also appears that only two thirds of the estimated need of iron was given in the single, massive injection and that the therapeutic effect did not last for the two months of control.

Some of the cases have their own special interest because they

Days in relat. to injection	γ % SI	γ % TIBC	g % Hb
— 1	28	478	10.0
+ 6	96	—	11.7
+ 21	102	452	12.2
+ 33	90	425	12.2

Table 2.

Case 11. 2 year-old boy with celiac disease and slight iron deficiency anemia. The changes in serum-iron (SI) and total iron-binding capacity (TIBC) during the month following one single injection of 5 ml Intrafer (= 100 mg Fe). The values of the TIBC give a more adequate knowledge of a latent iron deficiency.

previously proved to be resistant to treatment by repeated and lengthy peroral iron therapy. A report of two such cases, each representing one of the two types of hemoglobin response will now be given. The first of these also showed the most noticeable toxic symptoms in the material.

Case No. 5.

A 15-month-old girl who weighed 1.600 g at birth. She was nursed in the premature ward and, after little more than a month, developed anemia which, in the beginning, was normochromic and then became hypochromic with a hemoglobin value of about 8 to 9 g%. In spite of intensive iron therapy per os which was carried out for practically the whole of her first year of life, there was no improvement. At times she reacted by vomiting, for which reason different iron preparations were used. For about two months before the actual treatment she had been getting 20 drops of "Guttafer" twice a day (= 70 mg Fe per diem). She was admitted here for parenteral iron therapy. Her weight was 9.000 g; she was small, delicate and pale. No epithelial symptoms. Otherwise there was nothing of interest in the status. The liver and spleen were not palpable. The blood values appear in table 1. Differential count showed a preponderance of lymphocytes but no immature cells. Erythrocytes presented a strongly pronounced anisocytosis and poikilocytosis. Price-Jones curve was broad with an average diameter of 6.6 μ . Tibial puncture revealed intensified erythropoiesis with numerous immature red cells which were partly megaloblastic in character. The erythrocytes presented a pronounced anisocytosis with rather many large megalocytic elements.

The girl was given two injections of "Intrafer", the first one being 4 ml (= 80 mg Fe), and the second 5 ml (= 100 mg Fe). On the first occasion her temperature rose to 38°.5 C on the same afternoon. Otherwise there was nothing of note. The second injection 10 days later brought on intense shivering after 3/4 of an hour, peripheral cyanosis and cold hands and feet, cold sweat and a pronounced general pallor similar to that seen in the beginning of a state of collapse. Notwithstanding, she was capable of screaming during the whole of this time and her general condition was never dangerous. She was given a stimulant of 0.4 ml Nicetamid. Half an hour later her colour improved and the extremities were warm. A couple of hours later she appeared quite unaffected, but had a temperature of 40°.5 C. The following morning there was nothing of note and she was afebrile. Hemoglobin remissions were good and rapid with a moderate reticulocyte summit. Diminished anisocytosis in the peripheral blood. A new tibial puncture showed, on the whole, a more mature erythropoiesis with only one or two cells that were megaloblastic in character. For this reason a total of 35 mg vitamin B₁₂ was given a good three weeks after the first injection of "Intrafer". Nevertheless a complete normalization of the bone marrow was not achieved during the following week. She was discharged from the hospital in an extraordinarily improved condition three weeks after the beginning of the treatment and had a hemoglobin value of 12.5 g % and 5.05 million red blood corpuscles. One month later a control examination was made and she was found to be in the same good state of health, with a hemoglobin value of 13.0 g %.

Case No. 10.

A 9 year-old boy with an early beginning and exceptionally severe form of celiac disease. He had had grave and threatening celiac crises, repeated states of tetany, negative balance of fat metabolism, muscular atrophies, skeletal changes together with typical psychic alterations. At the age of nine, he showed a physical development corresponding to a child of from 4 to 5 years of age. His body weight was 19 kg. Right from his early years he had had hypochromic anemia which, in the beginning, in any case, responded to oral iron therapy. At the age of six the boy was again admitted with a hemoglobin value of about 9 to 10 g %. On this occasion, and ever since, he no longer reacted well to iron per os, but instead was afflicted with increased gastro-intestinal trouble. For this reason treatment for anemia was avoided. During the half year prior to intravenous iron therapy, the anemia was markedly hypochromic with a colour index of between 0.6 and 0.7, and a hemoglobin value of between 7.5 and 9.5 g %. The red blood cell picture showed pronounced anisocytosis and poikilocytosis with a corpuscular diameter varying between 5.5 and 10.0 μ . The average diameter was 7.27 μ . The

reticulocytes were constantly about 30 to 40 per thousand. No bone marrow punctures were made due to the patient's violent psychic reactions to physical pain. Plasma proteins were low; during the last half year between 5 and 6 g %. The decrease primarily concerned the albumin, but nevertheless the albumin/globulin quotient was usually above 1.0. Prior to the "Intrafer" treatment he got, as a trial for two months, massive doses of B₁₂, in all 160 microgrammes. During the latter part of the time of treatment this was combined with oral iron therapy, all without having the slightest effect on the low blood values. On a previous occasion, folic acid had been tried as well, but with the same negative results. It was therefore decided to give iron intravenously. On account of the atypical way in which the patient reacted, as well as because of his sensitive constitution, the administration was carried out by means of intravenous drip; 10 ml "Intrafer" (= 200 mg Fe) was given in 350 cc 5 % glucose during the course of 4½ hours. No toxic reactions were noted. During the following two weeks there was only a slow increase of hemoglobin, and no increased reticulocytosis. Thereafter, there was a rapid increase of the reticulocytes which reached the maximum of 130 per thousand on the 19th day. There was still the same slow, but progressive increase of the hemoglobin content. During the follow-up examination two months after the treatment, the patient was in a surprisingly good condition. The hemoglobin value had increased to 11.9 g %, and the colour index has risen to 0.88. These values must be regarded as satisfactory, especially as he was given considerably smaller doses than the estimated need. Barely two weeks later, however, the boy entered into a new period of decline accompanied by edema, tetany, and a generally low state of health. After recovering from this, he again showed a fall in the blood values. Nevertheless, the hemoglobin now lay on a higher level than the year previously, viz. 10—11 g %, whereas the index remained at about 0.8.

Toxic effects: The unpleasant, incipient shock picture related above, fortunately seems to be rare, at all events if one keeps within moderate injection doses. From table 3 it appears that single massive doses can nevertheless be tolerated well by certain children, but that the risk seems to be considerably greater if one exceeds a dose of about 10 mg per kg body weight. In all probability, symptoms can even arise in individual cases with much smaller amounts, but under these circumstances the risk of a real state of shock ought to be minimal. It is believable that there is some connection between the tolerance capacity and the size of the iron-binding capacity. It should therefore

Table 3.

Toxic manifestations after intravenous injections of saccharated oxide of iron (Intrafer) in single doses.

Mg Fe injected per kg body wt.	Number of injections	Local reactions (thrombo- phlebitis)	On injection slight toxic manifestations Flushing Cough Tiredness	1-4 hrs Mode- rate toxic mani- festations Nausea Paleness Shivering Temp. 39° C	3/4 hr Strong toxic manifesta- tions Incipient shock Pale cya- nosis Shivering Temp. > 40° C.	Vasovagal Shock
0-5	6	0	0	0	0	0
5-10	20	1	1	0	0	0
10-20	8	0	0	3	1	0

be emphasized that large single massive doses have, in these cases, mostly been given to children with sideropenia, that is to say with a considerably raised value for the iron-binding capacity. Another possibility is that the growing organism may be incapable of breaking down the saccharated oxide of iron complex as quickly as some adults. However, very little, if anything at all, is known about the mechanism of the intoxication symptoms. Under such conditions, one may well ask if it is necessary to give single massive doses as has been done in this case. Naturally, it is not necessary, but for technical and psychological reasons it is especially important to avoid giving irritating, daily doses, at all events, to the smaller children. In cases where one has reason to be especially careful, it would be preferable to resort to an intravenous drip using a 5 % glucose vehicle as the dilution medium.

It would appear that toxic symptoms have a tendency to make their appearance between one and four hours after the injection. There was only one case that showed any sort of reaction in connection with the actual injection, and only an extremely mild one at that. This was a girl of 1 year of age, who had a general flushing of the skin and a slight irritable cough. The manifestations that appeared later began with pallor, a cold sweat and a rather severe attack of shivering (cases 4, 5 and 17), followed by a rapid transitory high temperature of about 40°C. Of these three cases it was only Case 5, as previously reported,

who manifested an alarming circulatory insufficiency. In all three, however, the symptoms subsided during the course of an hour or so. Over and above these palpable general symptoms it is to be noted that a boy suffering from a troublesome nephritis (case 19) showed an increased hematuria — though only during the day following a moderately large single injection. Notwithstanding, there were a number of other cases that had been given considerably larger single massive doses who showed normal sediments many hours and days after the injections. No eosinophilia in connection with single or repeated doses has been observed.

The other aspect of the intoxication problem, i. e. any eventual late manifestations in connection with too large a total dose of iron, has not yet been fully investigated. Only a few autopsies of cases treated with saccharated oxide of iron have, so far, been published. The lapse of time after the last injection has in no case been more than a couple of months. Hitherto, none of the cases have shown any beginning fibrosis or other damage to the parenchymal organs. Experiences with experimental animals speaks in favour of pure iron preparations as relatively inert, even in large doses. BROWN, MOORE and others (1950) have given dogs up to 1,000 mg iron per kg body weight without any signs of cirrhosis 15 months after the treatment. ANDERSSON (1950) came to the same conclusions in his observations of 110 rabbits. Thus it seems reasonable to think that iron, while important, is probably not the only etiologic factor in producing the symptomatic form of hemochromatosis, such as occurs after repeated transfusions.

One case in the author's material died from an intercurrent disease six weeks following a vigorous and fully completed treatment. The results of the autopsy are of special interest as exceptionally massive doses of saccharated iron had been given.

Case No. 9.

A boy, aged 1 year and 2 months, weighing 7 kg; scaphocephalic and grossly underdeveloped. He was previously a patient in the Children's Department on account of transient but recidivating cystopyelitis. Hypochromic anemia noted half a year previously. Hematologically examined

while in an uninfected state one week after his last short pyelitic incident, and treated with large doses of "Intrafer" as a considerable iron deficiency was observed (see Table 1). Rapid powerful hemoglobin remissions. Sent home, in a decidedly improved state of health all things considered. He remained so for the next six weeks but died suddenly from an acute hyperpyretic climax which, in all probability, was a relapse of cysto-pyelitis.

Autopsy diagnosis (Dr. Ingrid Lingmark): Pyelonephritis chronica + Bronchitis acuta + Bronchopneumoniae.

Histologic examination showed a profusion of hemosiderin in the reticuloendothelial cells in the spleen, only a moderate amount in the Kupffer cells and no damage to the parenchymal cells of the liver (see Fig. 4). Negative iron staining of preparations from the kidneys, lungs and pancreas. Bone marrow, nothing of note.

Quantitative chemical determination (Dr. Bo Hallgren): See Table 4.

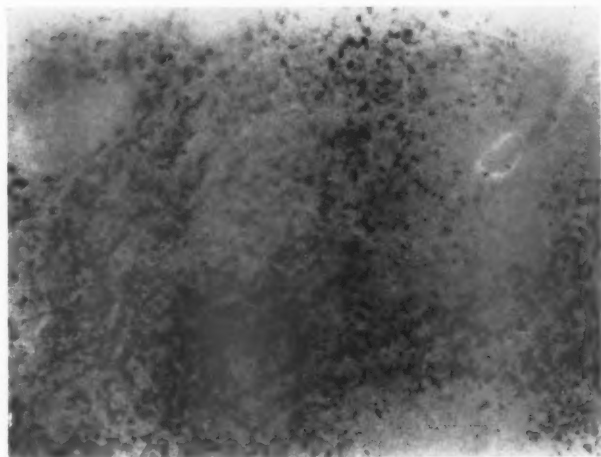
Up to the present, then, no proof has been found of pathologic parenchymal changes even from very vigorous intravenous iron therapy. On the other hand, the longest time of observation has been little more than one year, even in respect to experiments carried out on animals. It is therefore necessary to exercise care in regard to the total amount of iron injected. Possibly, the risks have been exaggerated.

3. Indications for the use of saccharated oxide of iron in children

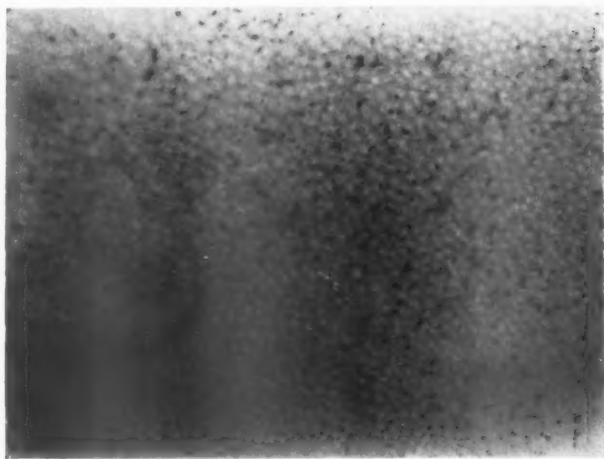
Since the response of patients with iron deficiency anemia to oral iron therapy usually is good, there are few real indications for giving iron intravenously. For practical and psychological reasons, this especially applies to children. Under certain conditions, however, one may talk about definite indications, namely in iron-deficient children who

1. are unable to derive full benefit from iron administered orally as for instance in celiac disease.
2. cannot tolerate oral iron therapy without nausea, diarrhea, etc.
3. must have their intestines shielded from every conceivable mucosal irritant, e. g. in ulcerative colitis.

Sometimes it may also be considered advisable to give an initial single massive dose of iron intravenously in cases of severe



A



B

Fig. 4. Case 9. Iron granules in spleen (*A*) and liver (*B*).

Table 4.

Case 9. Quantitative chemical determinations of hydrolyzable iron in some organs. (The values received from Dr Bo Hallgren, Institute of Medical Chemistry, Uppsala, who performed these analyses.)

Organ	Weight in g	Mg Fe per 100 g organ (fresh weight)	Total amount Fe in mg
Liver	207	40	82.8
Spleen	13	99	12.9
Kidneys ...	26	3.4	0.9
Lungs	148	2.0	3.0
Heart	34	1.9	0.7

but uncomplicated iron deficiency anemia of the nutritive type. By doing so, one may achieve an improvement in the patient's general condition and the hemoglobin value more quickly than otherwise.

There is no real reason to anticipate any hematological improvement in cases of anemia during the actual course of infection. SINCLAIR and DUTHIE (1949), however, have achieved remarkably good results in adults suffering from long standing rheumatoid arthritis with hypochromic anemia, resistant to previous oral iron therapy. There are, however, contradictory investigations on anemias of infection from other sources (18), and so, for the time being, this indication should be accepted with reservation.

In summary it may be said:

that saccharated oxide of iron is a valuable therapeutic in pediatrics within a limited range of indications,

that the hemoglobin remissions after treatment with saccharated oxide of iron in iron-deficient children are marked and rapid,

that children usually seem to tolerate proportionally large single doses of saccharated oxide of iron (Intrafer) quite well, up to about 10 mg per kg body weight,

that children up to the age of 2—3 years can, for practical and psychological reasons, be beneficially treated by giving single injections, not exceeding 10 mg per kg body weight,

that older children are more satisfactorily treated by repeated and somewhat smaller doses such as, for example, 5 mg per kg body weight at a time,

that sensitive cases, as well as those in need of very large total amounts of iron, should be given saccharated oxide of iron by means of a slow intravenous drip with 5 % glucose.

Finally, that care should be taken in regard to the total amount of iron injected. One should therefore keep within the estimated need of iron until many years of observation have proved the harmlessness of very large iron depots, and the beneficial, long lasting effect on a previously sideropenic organism.

Summary

The behaviour of saccharated oxide of iron in the blood is discussed. In addition to uptake and conversion of the iron complex in the reticulo-endothelial cells, an increasing saturation of the iron-binding capacity during the first few hours following intravenous injection may indicate a liberation of soluble iron directly in the blood. Therapeutic trials with a Swedish preparation of saccharated iron (Intrafer, *Pharmacia*) are reported. Twentyone children with anemia, mainly of iron deficiency type, were studied. The diagnosis of iron deficiency was substantiated by a decreased colour index, a low serum iron and an increased iron-binding capacity of the serum. In all cases free from infection good hemoglobin responses were obtained. Among these were two cases who had not responded to long periods of oral iron treatment. The preparation was well tolerated in amazingly large single doses. Thus, repeated venipunctures often could be avoided. A few toxic reactions after massive doses (more than 10 mg Fe per kg body weight) were observed. The question of possible late toxic manifestations on the parenchymal organs is discussed. The indications for the use of intravenous iron in childhood are set forth and a scheme for the calculation of the approximate need of iron is given.

La thérapeutique par le fer intraveineux en pédiatrie.

L'auteur traite de la destinée dans le sang d'un oxysaccharide de fer. Outre un dépôt et une transformation d'un complexe ferreux dans le système réticuloendothélial, on peut observer, pendant les premières heures qui suivent une injection intraveineuse, une saturation croissante de la capacité de fixation du fer par libération de fer directement dans le sang. On rapporte une expérience thérapeutique faite avec un sac-

charide de fer, préparé en Suède (Intrafer, Pharmacia). Vingt et un enfants, avec anémie, essentiellement de type ferriprive, ont été observés. Le diagnostic de carence en fer repose sur une diminution de la valeur globulaire, un taux bas de fer dans le sérum et une capacité croissante de fixation de fer. Dans tous les cas sans infection, de bons taux d'hémoglobine ont été atteints. Parmi ceux-ci, se trouvaient deux cas qui n'avaient pas réagi à un traitement per os de longue durée. De façon surprenante, de grosses doses isolées de la préparation ont été bien supportées. Ainsi, des ponctions veineuses répétées ont pu être évitées. Après de grosses doses (de plus de 10 mg de Fe par kilo) quelques signes toxiques ont été observés. La possibilité d'une action toxique tardive sur les organes parenchymateux est discutée. Les indications de l'emploi du fer intraveineux chez l'enfant sont données, ainsi qu'un schéma pour le calcul des besoins approximatifs.

Die intravenöse Eisentherapie in der Kinderheilkunde.

Es wird das Verhalten von Eisenoxysaccharat im Blute besprochen. Neben einer Aufnahme und Verwandlung des Eisenkomplexes in den retikulo-endothelialen Zellen kann eine zunehmende Sättigung der Eisenbindungsfähigkeit während der ersten Stunden nach intravenöser Injektion auf eine Dissoziation von löslichen Eisen direkt im Blut hinweisen. Es wird über therapeutische Versuche mit Anwendung eines schwedischen Eisensaccharatpräparates (Intrafer, Pharmacia) berichtet. Einundzwanzig Kinder, mit Anämie, hauptsächlich vom Eisenmangeltypus, wurden beobachtet. Der Eisenmangel wurde durch verminderten Farbenindex, niedrige Eisenwerte und eine gesteigerte Eisenbindungsfähigkeit des Serums diagnostiziert. In allen infektionsfreien Fällen wurden gute Hb-Werte erreicht. Darunter befanden sich zwei Fälle, bei welchen eine langdauernde perorale Behandlung nicht gewirkt hatte. Erstaunlich grosse Einzelgaben des Präparates wurden gut vertragen. Auf diese Weise konnten wiederholte Venenpunktionen vermieden werden. Nach grossen Gaben (von mehr als 10 mg Fe pro kg Körpergewicht) wurden einige toxische Auswirkungen beobachtet. Es wird die Möglichkeit einer späteren toxischen Auswirkung auf die parenchymatösen Organe besprochen.

Es wird die Indikation für den intravenösen Eisengebrauch im Kindesalter angegeben und ein Schema zur Berechnung des annähernden Bedürfnisses an Eisen mitgeteilt.

Terapéutica con hierro intravenoso en pediatría.

Se discute la acción del óxido de hierro sacarado en la sangre. Al lado de un aumento y conversión del complejo férrico en las células reticuloendoteliales, un aumento de la saturación de los depósitos férricos

durante las primeras horas siguientes a la inyección intravenosa puede indicar la liberación de hierro soluble directamente en la sangre. Se comunican los efectos obtenidos con la administración de un preparado de hierro sacaratado sueco (intrafer Pharmacia). 21 niños afectos de anemia primordialmente de tipo ferropénico han sido estudiados. El diagnóstico de deficiencia de hierro se comprobó por una disminución del valor globular, hierro sérico bajo. En todos los casos, excluidas por otra parte las infecciones asociadas, los valores de respuesta de la hemoglobina fueron buenos. Entre estos casos hubo 2 que no habían respondido a la administración durante largos períodos de hierro por vía oral. Los preparados son tolerados de un modo sorprendente a dosis amplias aisladas, por otra parte las punciones venosas repetidas frecuentemente deben evitarse. Se observó un escaso número de reacciones tóxicas tras la administración de dosis masivas (mas de 10 mg. de hierro por kilo de peso corporal). Se discute la cuestión de las posibles manifestaciones tóxicas tardías sobre los órganos parenquimatosos. Se sintetizan las indicaciones de uso de la terapeutica intravenosa con hierro en la infancia, y se aporta un esquema para el cálculo aproximado de las necesidades en hierro.

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PROGRESS IN PEDIATRICS

Die Ätiologie der Enzephalomeningitis bei Kindern, besonders des Syndromes der akuten abakteriellen (aseptischen) Meningitis

von

ARVID WALLGREN, Stockholm

In Schweden sowie in den übrigen skandinavischen Staaten traten in den zwanziger Jahren akute Enzephalomeningitiden gehäuft auf. Sie kamen vor ohne epidemiologischen Zusammenhang mit der Enzephalitis lethargica oder den beiden damals bekannten Enzephalitis verursachenden Viruskrankheiten, Poliomyelitis und Parotitis. Durch eigene persönliche Erfahrungen und aus dem Schrifttum konnte ich eine Reihe Beobachtungen über eine Art von gutartiger Enzephalomeningitis sammeln, die ich als eine Krankheit *sui generis*, wahrscheinlich von Virusnatur, betrachtete. Die Gründe hierfür waren folgende:

Es handelte sich dabei um eine infektiöse Krankheit in den Meningen, welche bisweilen in epidemischer Form auftrat. Ihr klinisches Bild war an verschiedenen Orten und bei verschiedenen Gelegenheiten so gleichförmig, dass es in hohem Grade wahrscheinlich erschien, dass man es hier mit einer und derselben Erkrankung zu tun hatte. Nach den damaligen Feststellungen schien diese Krankheit nicht an eine und dieselbe bekannte Infektionskrankheit des zentralen Nervensystems gebunden zu sein. Daher war es möglich, dass es sich hier um eine bisher nur wenig bekannte selbständige Infektionskrankheit des zentralen Nervensystems handelte. Die Fälle, die zu dieser Krankheit gerechnet wurden, zeichneten sich durch folgende Kriterien aus: 1. Akuter Beginn mit deutlichen meningitischen Symptomen. 2. Meningitische Veränderung der Spinalflüssig-

keit, schwankend zwischen nur unbedeutender Vermehrung der einkernigen Zellelemente und Trübung durch Leukozyten. 3. Steriler Liquor sowohl bei direkter Untersuchung als auch bei Kulturversuch. 4. Relativ kurzer Verlauf, gutartig, ohne sekundäre Komplikationen. 5. Fehlen einer nachweisbaren Ätiologie, sowohl in Form lokaler Affektionen (Otitis, Sinusitis, Trauma etc.) als auch in Form einer Allgemeinerkrankung (akute oder chronische Infektionskrankheiten) 6. Fehlen von epidemiologischen Beziehungen zu einer meningitiserzeugenden Infektionskrankheit.

Die Krankheit wurde akute aseptische Meningitis genannt und als eine neue Infektionskrankheit des Zentralnervensystems aufgefasst. Dieser Name wurde von vielen Seiten mit Recht kritisiert, und man schlug eine Reihe anderer Benennungen vor: seröse Meningitis, benigne lymphozytäre Meningitis, abakterielle Meningitis und so weiter. Mit aseptisch hatte ich gemeint, dass keine Bakterien im Spiele waren; abakteriell ist ohne Zweifel besser. Die Bezeichnung seröse Meningitis fand ich nicht gut, weil die Spinalflüssigkeit bisweilen eitrig aussehen kann. Benign ist auch ein Epithet, das nicht ganz glücklich erscheint, da die Krankheit in Ausnahmefällen zum Tode führt.

Die klinischen, und epidemiologischen Erfahrungen der letzten 27 Jahre sowie die Fortschritte der Bakteriologie und Serologie haben gezeigt, dass mehrere heutzutage feststellbare Erreger dasselbe Krankheitsbild erzeugen können. Es ist daher besser, statt von einer Krankheit *sui generis* von einem Syndrom zu sprechen. Die Erfahrung hat auch gelehrt, dass es unmöglich ist, mit Sicherheit zwischen Meningitis und Enzephalitis zu unterscheiden, und viele der hierhergehörigen Krankheiten weisen bisweilen auch enzephalitische Züge auf. Am besten wäre es daher vielleicht, von dem Syndrom oder dem Krankheitsbild der akuten abakteriellen Enzephalomeningitis zu sprechen.

Nach meiner ersten Mitteilung im Jahre 1924 kamen aus verschiedenen Gegenden der Welt Berichte über Beobachtungen von ähnlichen Erkrankungen. Alle diese Fälle, die entweder einzeln oder gehäuft auftraten, entsprachen in ihrer Symptomatologie und im übrigen den Kriterien, die aufgestellt worden

waren. Nun, diese Kriterien sind nicht derart spezifisch, dass sie als pathognomonisch für eine Krankheit *sui generis* betrachtet werden können. Es war schon von Anfang an klar, dass sich unter diesem Krankheitsbilde mehrere, ätiologisch verschiedene Enzephalomeningitiden verbergen könnten. Schon früh wurde an die Enzephalitis lethargica, die aparyalytische Poliomyelitis und die Mumpsmeningitis ohne nachweisbare Speicheldrüsenentzündung gedacht. In einzelnen Fällen war es natürlich wohl möglich, dass diese oder eine andere bekannte Ätiologie vorliegen konnte. Aber, wenn die Krankheit gehäuft auftrat ohne Beziehung zu gehäuften Auftreten von typischen Fällen anderer diagnostizierbarer Erkrankungen, war es unwahrscheinlich, dass diese abakterielle akute Meningitis einer dieser letztgenannten Krankheiten ätiologisch zugehörte. Die Entdeckungen der letzten zwei Jahrzehnte haben nun viel zur Beleuchtung der Ätiologie der akuten abakteriellen Meningitis beigetragen.

Man hat eine Reihe verschiedener Einteilungen der Enzephalomeningitiden vorgeschlagen. Eine allgemein anerkannte Klassifizierung gibt es einstweilen nicht. Das Beste wäre vielleicht eine ätiologische Einteilung, doch ist unser Wissen in dieser Hinsicht hierfür noch zu lückenhaft. Krankheiten, die man vor einem Jahrzehnt als identisch betrachtete, weil sie klinisch einander glichen und sich ähnlich entwickelten, sind, wie man nun weiss, ätiologisch ganz verschieden. So wird uns die Zukunft wahrscheinlich auch zeigen, dass ein Krankheitsbild, welches wir jetzt als eine nosologische Einheit ansehen, durch zwei oder gar mehrere ätiologisch ganz verschiedene Erkrankungen hervorgerufen sein kann. Die Einteilung, die ich hier benutze, ist deshalb nur als eine provisorische zu betrachten. Es muss hervorgehoben werden, dass es Zwischenfälle gibt, die sowohl in die eine wie in die andere Gruppe einpassen.

Schema der abakteriellen Enzephalomeningitiden

I. Viruskrankheiten.

A. Sekundäre Enzephalomeningitiden.

1. Masern
2. Röteln

3. Wasserpocken
 4. Pockenimpfung
 5. Andere Krankheiten.
- B. Primäre neutrope Enzephalomeningitiden.
- a. Die Enzephalomeningitis als fakultative Erscheinung.
 1. Poliomyelitis
 2. Parotitis
 3. Herpes-Infektionen
 4. Andere Krankheiten.
 - b. Die Enzephalomeningitis als obligate Erscheinung.
 1. Enzephalitis lethargica
 2. Akute lymphozytäre Choriomeningitis
 3. St. Louis-Enzephalitis
 4. Westliches Pferde-Enzephalitis-Virus
 5. Östliches Pferde-Enzephalitis-Virus
 6. Japanische B-Enzephalitis
 7. Russische Wald-Frühling-Enzephalitis
 8. Cocksackie-Virus-Erkrankungen
 9. Andere, noch unbekannte Krankheiten.
- II. Leptospirose.
1. Weilsche Krankheit
 2. Schweinehüterkrankheit
 3. Canicola-Enzephalitis
 4. Andere Leptospirose.
- III. Andere Erreger.
1. Toxoplasmose
 2. Torulose
 3. Rickettsien?
 4. Andere Krankheiten.

Die meisten akuten primären Enzephalomeningitiden gehören ätiologisch zu den Viruskrankheiten. Ein grosser Teil der übrigen ist durch Leptospireninfektionen hervorgerufen. Der Rest ist ein Sammeltopf von Krankheiten, die als Ausdruck ganz verschiedener Arten von Erregern in Ausnahmefällen vorkommen können. Somit kann man die primären akuten abakteriellen

Enzephalomeningitiden in drei Hauptgruppen einteilen: I. Viruskrankheiten. II. Leptospirosen. III. Durch andere Erreger verursachte Krankheiten.

I. Viruskrankheiten

Einige der Virus-Enzephalomeningitiden sind in den klassischen Fällen durch ihr charakteristisches Krankheitsbild und/oder durch typische Organsymptome gekennzeichnet. Die Enzephalomeningitis ist eine Begleiterscheinung, die nur fakultativ zum Krankheitsbilde gehört. Der Erreger hat einerseits Affinität zum Gehirn und zu den Meningen, andererseits zu anderen Organen oder Organsystemen. Bisweilen kommen diese zwei Hauptlokalisationen beide vor, bisweilen nur die eine. Hiernach kann man die akuten primären neutropen Virusenzenzephalomeningitiden in zwei Hauptgruppen einteilen, je nachdem die Enzephalomeningitis fakultativ oder obligat im Krankheitsbilde auftritt. Zur ersten Gruppe gehören die Poliomyelitis, die Parotitis und die Herpesinfektionen sowie einige andere Viruserkrankungen (infektiöse Mononukleose, Lymphogranuloma inguinale und andere). Bei allen diesen Enzephalomeningitiden können die klinischen Krankheitserscheinungen auf die Infektion des Zentralnervensystems beschränkt sein und entsprechen dabei in ihrem Auftreten dem Syndrom der akuten abakteriellen Meningitis. Es ist nicht möglich, sie nur klinisch voneinander zu differenzieren; die ätiologische Diagnose muss die Aufgabe der Virologie und der Sero-logie sein.

a. Fakultative neutrope Virus-Enzephalomeningitiden

1. Die Poliomyelitis

Das Poliomyelitisvirus war immer als Erreger des Syndroms der akuten abakteriellen Meningitis verdächtig. Zu Epidemiezeiten kommen aparalytische Fälle vor, die sich wie eine benigne lymphozytäre Meningitis verhalten und klinisch nicht von anderen Fällen des Syndroms zu unterscheiden sind. Bei gewissen Epidemien waren diese Fälle von aparalytischer Poliomyelitis sehr gering an Zahl bei anderen waren sie viel frequenter als die

typischen Fälle der Krankheit. Der epidemiologische Zusammenhang und positive Impfungsversuche an Affen sprachen für Poliomyelitisgenese dieser Fälle.

Die Frage der Ätiologie der aparalytischen Poliomyelitisfälle ist jedoch in ein anderes Licht gerückt worden, seitdem DALLDORF und SICKLES 1947 in zwei Fällen, die während einer Poliomyelitisepidemie auftraten und als aparalytische Poliomyelitis aufgefasst wurden, ein anderes, mäusepathogenes Virus nachgewiesen haben. Dieses sogenannte Coxsackievirus ist nachher vielenorts isoliert worden. Ich werde später auf dasselbe zurückkommen. An dieser Stelle möchte ich nur hervorheben, dass man zur Zeit noch nicht weiss, welche Rolle das Coxsackievirus beim Auftreten von aparalytischer Poliomyelitis spielt, ob Interferenzphänomene von Bedeutung sind oder nicht. Jedenfalls kommen aparalytische Fälle von Poliomyelitis vor, bei denen Infektion mit dem Coxsackievirus virologisch oder serologisch nicht feststellbar ist. Das Poliomyelitis virus muss daher wie bisher als einer der wichtigsten Erreger des Syndroms der akuten abakteriellen Meningitis aufgefasst werden.

2. Die Parotitis epidemica

Die epidemische Parotitis ist sehr oft von Symptomen seitens des Zentralnervensystems begleitet. In den meisten Fällen handelt es sich um Meningitis, in seltenen Fällen um Enzephalitis oder Enzephalomeningitis. Die Frequenz der Mumpsenzephalomeningitis kann nicht ausschliesslich nach den klinischen Erscheinungen in Mumpsfällen beurteilt werden. Diese Erkrankung kommt sehr oft auch ohne klinische Meningitissymptome vor, und nur eine systematisch durchgeführte Lumbalpunktion aller Mumpskranken gibt die wahre Frequenz der Mumpsmeningoenzephalitis an. ALM hat über eigene Erfahrungen und die anderer Autoren berichtet: unter 661 systematisch lumbalpunktierten Fällen aus drei Epidemien von epidemischer Parotitis kam Pleozytose der Spinalflüssigkeit in 55 % der Fälle vor, von denen nur etwa die Hälfte klinische Meningitissymptome zeigte. Die Häufigkeit von Meningoenzephalitis bei Mumps scheint in gewissen Epidemien viel grösser zu sein als in anderen. Die Sympto-

me treten im allgemeinen (70 %) kurz nach der Parotitis auf, bisweilen kurz vor, gleichzeitig mit oder längere Zeit, bis mehrere Wochen, nach der Parotitis.

In gewissen Fällen kommt eine Mumpsenzephalomeningitis ohne Speicheldrüsenentzündung vor. Dies hat man bei epidemiologischem Zusammenhang mit typischen Fällen von Parotitis, z. B. bei Geschwistererkrankungen, schon lange gewusst. Diese Fälle entsprechen ganz dem Syndrom der akuten abakteriellen Meningitis, und es war naheliegend sich vorzustellen, dass es sich wenigstens bei einem gewissen Teil der hierhergehörenden Kranken um sporadische Fälle von Mumpsmeningitis handelte. Seitdem man nunmehr die Parotitisinfektion virologisch (JOHNSON und GOODPASTURE 1934) und serologisch (ENDERS und COHEN 1942) diagnostizieren kann, hat sich die Richtigkeit dieser Vorstellung bestätigt. Es hat sich herausgestellt, dass die Parotitisinfektion viel verbreiteter war, als man früher gedacht hatte, dass viele Personen spezifische Antikörper beherbergten, ohne je an typisches Mumps erkrankt zu sein.

Man nahm nun an, dass das Syndrom der akuten abakteriellen Meningitis oder wenigstens die meisten hierhergehörenden Fälle durch Parotitisinfektion hervorgerufen waren. Serologische Untersuchungen in New York, Washington und Gotenburg zeigten, dass steigende Antikörpertiter des Blutes in 29 %, 15 % respektive 7 % unter den akuten abakteriellen Meningitiden vorkamen. Die erstgenannte Gruppe bestand meist aus Kindern, und wenn diese Erfahrung verallgemeinert werden darf, würde die Erkrankung bei etwas weniger als einem Drittel von Kindern mit akuter abakterieller Meningitis durch das Parotitisvirus verursacht sein. Die Verhältnisse sind jedoch an verschiedenen Orten und zu verschiedenen Zeiten zu wechselnd, um einen solchen Schluss zu erlauben. Jedenfalls kann man nunmehr auch in sporadischen Fällen von akuter abakterieller Meningitis beweisen oder ausschliessen, dass die Parotitisinfektion eine ätiologische Rolle spielt.

3. Die Herpesinfektionen

Bei gewissen Fällen von Herpes simplex hat man schon lange Meningitis oder Enzephalomeningitis als Begleiterscheinung beobachtet. Diese zentralnervöse Krankheit entspricht im allgemeinen dem Syndrom der gutartigen akuten abakteriellen Meningitis. Nach Isolierung des Virus hat sich, besonders auf Grund serologischer Untersuchungen über spezifische Antikörper, die Auffassung von dem Vorkommen der Herpesinfektionen in der Bevölkerung gänzlich verändert. Es hat sich herausgestellt, dass etwa drei Viertel der erwachsenen Menschen ständig spezifische Herpes-Antikörper beherbergen. Der Nachweis neutralisierender oder komplementfixierender Antikörper gegen das Herpesvirus besagt daher sehr wenig hinsichtlich der Ätiologie einer vorhandenen Enzephalomeningitis. Für die Feststellung einer Herpesinfektion als Ursache einer Krankheit ist es nötig, entweder eine Steigerung des Antikörpertiters nach der Krankheit oder das Virus selbst nachzuweisen.

Die Isolierung des Herpesvirus aus dem Liquor soll jedoch auch bei normalen Menschen sowie bei Fällen von Enzephalomeningitis, die offenbar eine andere Ätiologie haben, gelungen sein. Die ätiologische Bedeutung des Virusnachweises ist daher noch eine offene Frage. ALM der sich viel mit Studien über die Herpesinfektion beschäftigt hat, ist es indes nur einmal bei 450 untersuchten Personen geglückt, das Herpesvirus aus dem Liquor zu isolieren, und in diesem Falle sprach auch die Antikörpersteigerung dafür, dass die Herpesinfektion eine ätiologische Rolle spielte. In fünf anderen Fällen von primärer akuter abakterieller Enzephalomeningitis hat er durch Feststellung von Antikörpersteigerung wahrscheinlich gemacht, dass die Krankheit durch eine Herpesinfektion entstanden war.

Von Interesse ist, dass die aphthöse Stomatitis, die wenigstens bei Kindern (GARD) als Herpesinfektion zu betrachten ist, auch von einer lymphozytären, gutartigen Meningitis begleitet sein kann. Unter 204 Kindern mit abakterieller Meningitis fand ALM bei 12 (= 6 %) klinische Zeichen von Herpesinfektion oder aphthöser Stomatitis. Bei Erwachsenen war der Prozentsatz 1,5 %

(1 250 Personen). Er ist der Meinung, dass das Herpesvirus wahrscheinlich einen Teil der Fälle von akuter abakterieller Enzephalomeningitis hervorruft, eine Auffassung, der ich mich anschliesse.

4. *Andere fakultativ Enzephalomeningitis erzeugende Viruskrankheiten*

Ich möchte nur zwei der zur vierten Gruppe gehörenden fakultativen Enzephalomeningitiden kurz erwähnen, nämlich die infektiöse Mononukleose und den Herpes zoster.

Allem Anschein nach ist die infektiöse Mononukleose eine Viruskrankeheit, deren Erreger noch nicht isoliert ist. Sie ist keine seltene Erkrankung bei Kindern. Seit langem weiss man, dass sie mit den Symptomen einer akuten benignen Meningitis verlaufen kann. Mehr als 50 Fälle sind veröffentlicht worden (BERNSTEIN und WOLFF). Bisweilen kommt Pleozytose der Spinalflüssigkeit ohne klinische Meningitiserscheinungen vor. Die für die infektiöse Mononukleose typischen Symptome können sehr wenig ausgeprägt (Drüsen- und Milzschwellung) oder nur durch Blutuntersuchung feststellbar sein (Mononukleose, Paul-Bunnells Reaktion) und dann leicht übersehen werden. Die Ätiologie einer begleitenden Meningitis kann daher auch leicht unentdeckt bleiben, wenn man die morphologische Blutuntersuchung und den Paul-Bunellschen Test unterlässt. Bei Kindern scheint Begleitmeningitis seltener zu sein als bei Erwachsenen.

Das Virus, welches den Herpes zoster verursacht, scheint mit dem Varizellen-Virus verwandt zu sein, ist jedoch mehr neutrop als dieses. Bei Herpes zoster ist mehrfach Meningitis beobachtet worden, bisweilen nur lymphozytäre Pleozytose ohne klinische meningitische Symptome. Es ist sehr wahrscheinlich, dass das Zoster-Virus auch eine ätiologische Rolle beim Entstehen einer akuten abakteriellen Meningitis spielen kann.

b. *Obligate Virus-Enzephalomeningitiden*

Ich gehe nun zu den obligaten Virusenenzephalomeningitiden über. Sie scheinen für Europa weniger Interesse zu haben als die soeben besprochenen fakultativen. Ich werde mich beson-

ders bei denen aufhalten, die in unserem Erdteil nachgewiesen sind und noch vorkommen.

1. *Die Enzephalitis lethargica*

Die epidemische Enzephalitis von v. ECONOMO will ich nur kurz streifen. Seitdem die Pandemie dieser Krankheit nach dem ersten Weltkrieg aufgehört hat, ist die Erkrankung gradweise seltener geworden und scheint nun fast verschwunden zu sein. Daher ist das noch unbekannte Virus dieser Enzephalitis heute von geringer Bedeutung als Erreger von Enzephalomeningitiden. Die in den klassischen Fällen charakteristischen Symptome, der typische Verlauf und die fast immer vorhandenen zerebralen, besonders extrapyramidalen Folgekrankheiten, ermöglichen es im allgemeinen, diese Fälle von den anderen Enzephalomeningitiden zu unterscheiden, von denen später die Rede sein wird.

Neben ausgeprägten Krankheitsbildern kamen während der Epidemie auch wenig markante vor, darunter solche, die dem Syndrom der akuten abakteriellen Meningitis entsprachen. Das Virus der Enzephalitis lethargica gehörte daher zu den Erregern, die damals als Ätiologie der akuten abakteriellen Meningitis betrachtet wurden. Die Abwesenheit der für die lethargische Enzephalitis charakteristischen und gewöhnlichen Nachkrankheiten macht es indessen sehr unwahrscheinlich, dass die von Economo'sche Krankheit etwas mit diesem Syndrom zu tun hatte. Heutzutage scheint jedenfalls die Enzephalitis lethargica keine oder eine sehr unbedeutende Rolle mehr zu spielen.

2. *Die akute lymphozytäre Choriomeningitis*

Die zuerst isolierte Viruskrankheit, die in jeder Hinsicht dem Syndrom der akuten abakteriellen Meningitis entspricht, war die sogenannte akute lymphozytäre Choriomeningitis. Diese erstmalig in den Vereinigten Staaten beobachtete Meningitis war durch ihrem akuten Beginn, mässiges und kurzdauerndes Fieber, meningitische Symptome, lymphozytäre Spinalflüssigkeit, leichten Verlauf, benigne Prognose und oft gehäuftes Auftreten gekennzeichnet. Die Pleozytose des Liquors wechselt von ein

paar hundert bis ein paar tausend Zellen, hauptsächlich Lymphozyten. Die Krankheit dauert etwa ein bis drei Wochen.

Im Jahre 1934 gelang es ARMSTRONG und LILLIE, durch den Nachweis eines besonderen Virus zu zeigen, dass diese Krankheit artverschieden war von anderen bisher bekannten Meningitiden. Ihre Entdeckung wurde von anderen Autoren in verschiedenen Teilen Nordamerikas sowie in Europa (England, Frankreich, Holland, Deutschland, Ungarn, Rumänien und Russland) bestätigt.

Man sprach nun die Meinung aus, dass die Frage der Ätiologie der akuten abakteriellen Meningitis damit gelöst sei. Dies entsprach indes nicht der Wahrheit. In unserem Lande, wo man noch immer viele Fälle beobachtet, die dem Syndrom der akuten abakteriellen Meningitis entsprechen, hat man vergeblich versucht, das Armstrongsche Virus oder spezifische Antikörper bei Menschen und Nagetieren nachzuweisen (ALM, GARD). Dasselbe gilt von den meisten untersuchten Anhäufungen akuter abakterieller lymphozytärer Meningitis sowohl in Amerika als in Europa. Aus den Vereinigten Staaten liegen zwei Untersuchungen vor über das Vorkommen lymphozytärer Choriomeningitis unter Fällen, die dem Syndrom der akuten abakteriellen Meningitis entsprachen; SMADEL fand Choriomeningitis in 15 % und RASMUSSEN in 8,5 % der untersuchten Enzephalomeningitiden. In England hat MACCALLUM noch weniger, nur 3—5 %, gefunden.

Aller Wahrscheinlichkeit nach wird diese Krankheit nicht von Mensch zu Mensch übertragen. In fast allen Fällen von virologisch oder serologisch festgestellter Choriomeningitis hat man nachweisen können, dass Ratten im Haushalt der Erkrankten Armstrongsche Virus beherbergten. Diese Tiere werden als Zwischenwirt oder als Virusreservoir betrachtet. Die infizierten Ratten sind sehr lange Virusträger und scheiden das Virus mit den Faeces, dem Urin und dem Rachensekret aus. Wie es von hier auf Menschen übertragen wird, durch infizierte Lebensmittel, Einatmung von Rattenexkreten oder durch Insekten etc., ist noch unbekannt.

Das Virus kann nachgewiesen werden, indem man Blut, Spinalflüssigkeit oder Rachensekret intraperitoneal Meerschwein-

chen injiziert oder intrazerebral Mäusen einimpft. Komplement-bindende Antikörper sind zwei bis drei Wochen nach dem Beginn der Krankheit und neutralisierende Antikörper nach sechs bis acht Wochen oder länger nachweisbar. Bei Laboratoriumsinfektionen von Menschen betrug die Inkubationszeit fünf bis zehn Tage.

Serologischen Untersuchungen verdankt man neue Erfahrungen über die lymphozytäre Choriomeningitis. Es hat sich gezeigt, dass die Infektion mit dem Armstrongschen Virus viel verbreiteter ist, als man anfänglich glaubte, und sich auch bei Menschen feststellen lässt, die niemals mit Symptomen von Choriomeningitis erkrankt sind. So fand ARMSTRONG spezifische Antikörper in 11 % von Blutproben, die aus verschiedenen Gegenden Nordamerikas an sein Laboratorium gesandt worden waren.

Es hat sich herausgestellt, dass diese Virusinfektion bei Menschen auch andere Krankheiten als Meningitis hervorrufen kann, und zwar grippeähnliche Krankheitsbilder. In Ausnahmefällen entstehen sogar sehr schwere Enzephalitiden, die tödlich enden können. Es gibt somit alle Übergänge von grippeähnlichen Krankheiten mit oder ohne Pleozytose der Spinalflüssigkeit mit oder ohne andere neurologische Erscheinungen über leichte meningitische Krankheitsbilder, die bisweilen subklinisch verlaufen und nur lymphozytäre Pleozytose der Spinalflüssigkeit aufweisen, bis zu sehr schweren Enzephalitiden, die zum Tode führen können.

Die bisherigen Erfahrungen zeigen, dass das Armstrongsche Virus akute Enzephalomeningitiden erzeugen kann, die dem Syndrom der akuten abakteriellen Meningitis entsprechen. Dieses Virus kann aber nicht die alleinige Ursache des Krankheitsbildes sein, sondern ist nur einer der Erreger des Syndroms. Jedenfalls muss man immer an die Möglichkeit der akuten lymphozytären Choriomeningitis in allen den Fällen denken, die dem Syndrom der akuten abakteriellen Meningitis gleichen, und nach diesem Virus oder den spezifischen Antikörpern suchen.

3. *St. Louis-Enzephalitis*

Diese Krankheit trat zuerst 1933 in der Gegend von St. Louis auf und umfasste etwa 1000 Fälle. Im Gegensatz zu der Enzephalitis lethargica ist die St. Louis Enzephalitis gekennzeichnet durch plötzlichen Beginn, schnellen Verlauf sowie Fehlen oder sehr seltenes Vorkommen von Restsymptomen und Folgekrankheiten. Die Spinalflüssigkeit enthält bis zu 1000 Zellen, meist Lymphozyten. Die Sterblichkeit betrug etwa 20 % (LEAKE und Mitarbeiter). Ausser typischen Fällen wurden auch abortive Fälle konstatiert, die Ähnlichkeit mit der akuten lymphozytären Choriomeningitis, d. h. mit dem Syndrom der akuten abakteriellen Meningitis, hatten. Das Auftreten im Anschluss an die Epidemie, der Nachweis des Virus sowie komplementbindender oder neutralisierender Antikörper beweist die Zugehörigkeit dieser leichten Fälle zu der St. Louis-Enzephalitis.

Man wusste damals nicht, dass das nachgewiesene Virus auch bei Tieren vorkommt. Später (1940) konnte serologisch festgestellt werden, dass das Blut von Pferden Antikörper beherbergte, und dass das aus dem Menschengehirn gewonnene Virus nach Inokulation Enzephalitis bei Pferden hervorrief. Durch Antikörpernachweis ist auch wahrscheinlich gemacht, dass andere domestizierte und auch wilde Tiere infiziert sein können. Feststellung des Virus bei Mücken deutete auf die Übertragungsweise der St. Louis-Enzephalitis.

Obwohl diese Krankheit bisher in Europa nicht nachgewiesen ist, dürfte es doch ratsam sein, bei den europäischen Enzephalomeningitiden, auch bei Fällen, die das Syndrom der akuten abakteriellen Meningitis zeigen, nach dem Virus und den Antikörpern der St. Louis-Enzephalitis zu fahnden.

4. und 5. *Westliche und östliche Pferde-Enzephalitiden bei Menschen*

Ich komme nun zu vier anderen Virus-Enzephalomeningitiden, die auch als Tierkrankheiten bekannt sind, deren Erreger auf Menschen übertragen werden können. Nach Neutralisationstest zu urteilen, sind sie einander verwandt, aber artspezifisch. Hierher gehören die beiden Arten von Pferdeenzephalitis, die

West- und Ostenzephalitis in den Vereinigten Staaten, die japanische B-Enzephalitis und die in Russland vorkommende Wald-Frühling-Enzephalitis. Ob diese Enzephalitiden neue Krankheiten sind, die früher nicht bei Menschen auftraten, weiss man nicht genau; jedenfalls sind sie erst seit den dreissiger Jahren isoliert und serologisch identifiziert worden. Da sie bei uns in Europa bisher nicht nachgewiesen sind, werde ich ihre Klinik und Epidemiologie nur kurz streifen.¹

In den Vereinigten Staaten ist wahrscheinlich seit wenigstens 100 Jahren Enzephalitis bei Pferden vorgekommen. Die Krankheit wurde erst näher studiert im Anschluss an eine grosse Epidemie in Westamerika, in Kalifornien, im Jahre 1930. MEYER, HARING und HOWITT isolierten ein Virus aus dem Gehirn und Blut kranker Pferde. Drei Jahre später brach eine Epidemie von Pferdeenzephalitis in den östlichen Staaten von Nordamerika aus, und auch hier war es möglich, ein Virus nachzuweisen. Dieses war indes serologisch etwas von dem in der erstgenannten Kalifornien-Epidemie vorkommenden verschieden. Man sprach danach von West-Typus und Ost-Typus der amerikanischen Pferdeenzephalitis und hat diese beiden Virustypen bei verschiedenen Epidemien in Amerika immer wieder gefunden.

Im Anschluss an Epidemien von Pferdeenzephalitis wurden vereinzelte Fälle akuter Enzephalitis auch bei Menschen in derselben Gegend beobachtet. Man vermutete, dass diese Fälle durch dasselbe Agens hervorgerufen waren. Erst im Jahre 1938 konnte indessen das Virus der Ost-Enzephalitis bei Menschen nachgewiesen werden. Die Krankheit war sehr bösartig, die Sterblichkeit betrug etwa 75 %, und bei den meisten überlebenden fanden sich schwere neurologische Restsymptome. Kinder, namentlich Kleinkinder, waren besonders anfällig. Die klinischen Erscheinungen waren die einer schweren akuten Fieberkrankheit mit schnell eintretenden meningitischen und enzephalitischen Symptomen sowie mit mono- oder polynukleärer Pleozytose im Liquor.

Im gleichen Jahre, 1938, konnte man auch das Virus der

¹ Kurz nach dem ersten Weltkrieg trat in Frankreich eine Art von Pferdeenzephalitis auf.

West-Enzephalitis aus dem Gehirn von Menschen, die an Enzephalitis gestorben waren, identifizieren. Die Krankheit war in ihrem Auftreten und Verlauf weniger bösartig als die Ost-Enzephalitis. (Sterblichkeit etwa 20 %). Nach dem häufigen Vorkommen von Antikörpern gegen das West-Enzephalitis-Virus im Blute von Enzephalitisfällen im Westen zu urteilen, scheint diese Enzephalitis viel verbreiteter zu sein und häufiger bei Menschen aufzutreten. Später hat sich herausgestellt, dass nicht nur Pferde, sondern auch eine ganze Reihe von anderen domestizierten Säugern und Vögeln sowie wilde Tierspezies das Virus beherbergen können. Der Virusnachweis in Mücken und anderen Insekten macht es wahrscheinlich, dass die Krankheit durch diese übertragen wird.

6. *Japanische B-Enzephalitis*

In Japan hat man seit etwa 50 Jahren eine Art von Enzephalitis beobachtet, die einen ganz anderen Verlauf als die Enzephalitis lethargica (A-Enzephalitis der Japaner) hat. Im Jahre 1936 wurde das zugehörige Virus isoliert. Pferde und andere domestizierte sowie auch wilde Tiere sind infiziert, und die Übertragungsweise ist dieselbe wie bei den erwähnten Pferdeenzephalitiden. Am meisten erkranken Kinder. Der Verlauf und die Prognose der Krankheit entsprechen denen der St. Louis-Enzephalitis. Die japanische B-Enzephalitis ist die einzige der bisher hier besprochenen Enzephalitiden, von der man weiss, dass sie auch ausserhalb des Ursprungsortes beobachtet worden ist. Dieselbe Krankheit ist in verschiedenen Teilen von Australien epidemisch aufgetreten, wahrscheinlich durch Vögel aus Japan nach Australien verschleppt.

7. *Die russische Wald-Frühling-Enzephalitis*

Ebensolange wie die japanische Enzephalitis hat man in Russland eine Art von Enzephalitis beobachtet, die in Frühlings-epidemien verläuft und als Wald-Frühling-Enzephalitis bezeichnet wurde. Etwa drei Viertel der Erkrankten gaben an, dass sie ein bis zwei Wochen vorher von einem Insekt (Zeche) gestochen worden seien. Das Virus ist bei Menschen und bei vielen dome-

stizierten und wilden Tieren sowie bei verdächtigen Insekten in der Epidemiegegend festgestellt worden, und spezifische Antikörper sind bei den angegriffenen Menschen und Tieren nachweisbar. Das Virus ist artverschieden von dem der anderen hier erwähnten Enzephalitiden, zeigt aber viele Ähnlichkeiten mit dem St.Louis-Enzephalitisvirus.

Bisher ist noch unbekannt, ob eine oder mehrere dieser fünf letzterwähnten Enzephalitiden auch in Europa vorkommen. Jedenfalls liegt kein Bericht vor, dass das Virus oder spezifische Antikörper bei europäischen Enzephalomeningitiden nachgewiesen worden sind. Indes ist zu vermuten, dass sie durch infizierte Menschen, Vögel, Pferde oder andere Tierarten eingeschleppt werden können. Ebensowenig weiss man, ob andere der in Europa auftretenden Virus Enzephalitiden als die akute lymphozytäre Choriomeningitis Tierreservoir haben, und ob sie durch Insekten übertragen werden können.

8. Die Coxsackie-Virus-Erkrankungen

Hinsichtlich des Syndroms der akuten abakteriellen Meningitis ist eine Entdeckung der letzten Zeit von grosser Bedeutung, nämlich der Nachweis des Coxsackievirus (MELNICK, SHAW und CURNEN). Das Coxsackievirus oder das C-Virus, wie es nunmehr genannt wird, wurde erstmalig 1948 während einer Poliomyelitis-epidemie in dem kleinen amerikanischen Dorfe Coxsackie von DALLDORF und SICKLES bei zwei Kindern festgestellt, die an aparytischer Poliomyelitis erkrankt waren. Seither ist es oft und vielenorts, auch in Europa, als wahrscheinlicher Erreger von benignen Krankheiten des Zentralnervensystems gefunden worden. Diese Krankheiten ähneln bisweilen Fällen von akuter abakterieller Meningitis oder aparytischer Poliomyelitis.

Bei Laboratoriumsinfektionen treten nach einer Inkubationszeit von fünf Tagen kurzdauerndes Fieber und Muskelschmerzen auf. Lymphozytäre Pleozytose der Spinalflüssigkeit kommt vor, auch ohne klinische Meningitissymptome. Die Infektion wird wahrscheinlich durch Kontakt von Mensch zu Mensch übertragen und kommt offenbar sehr leicht zustande; Krankenschwestern, welche C-viruskranke Patienten pflegten,

wurden infiziert. Das C-Virus kann während der Krankheit aus den Faeces, dem Urin, dem Rachensekret, dem Liquor und Blut durch Impfung auf einige Tage alte Mäusesäuglinge isoliert werden. Nach der Krankheit kann man die C-Virusinfektion durch steigenden Antikörperspiegel im Blute nachweisen.

Auch bei uns in Schweden sind mehrere Fälle von gutartiger lymphozytärer Meningitis als C-Viruserkrankung bei Kindern festgestellt worden (MAGNUSSON, LINDAHL), und nach serologischen Untersuchungen (GARD) ist das Virus in der Bevölkerung ziemlich verbreitet. In 600 Fällen verschiedener Infektionen wurde das C-Virus fünfzehnmal von GARD isoliert. Unter Normalfällen wurde in der Schweiz von WIRTH und THELIN in 28 % positive Komplementfixationsreaktion gefunden. Es ist möglich oder vielleicht sogar wahrscheinlich, dass nicht nur viele Fälle, die man früher als aparalytische Poliomyelitis aufgefasst hat, sondern auch andere früher beschriebene Anhäufungen von ätiologisch nicht geklärter akuter abakterieller Meningitis durch das C-Virus hervorgerufen worden sind.

Die Zugehörigkeit der Enzephalomeningitis, die in gewissen Fällen der sogenannten Bornholmer Krankheit oder Myalgia epidemica auftritt, zu den C-Viruserkrankungen wird zur Zeit viel erörtert. Diese Krankheit ist sehr oft, vielleicht immer, von einer meningitischen Reaktion begleitet und kann als reine abakterielle Meningitis ohne die typischen Symptome (myalgische Schmerzen, besonders am Bauch und Rücken) vorkommen. Während der letzten Jahre hat man bei der Myalgia epidemica vielfach C-Virusinfektion mit oder ohne meningitische Erscheinungen durch Virus- oder Antikörpernachweis bewiesen (FINDLAY und HOWARD, WIRTH und THELIN, GABINUS und GARD). Bei 21 auf C-Virusinfektion untersuchten schwedischen Fällen von abakterieller Meningitis als Begleiterscheinung der Myalgia epidemica wurde diese Infektion siebenmal konstatiert. Serologisch beurteilt, scheinen alle Übergänge von typischer Myalgia epidemica ohne Liquorveränderungen bis zu voll ausgeprägter akuter Meningitis ohne die anderen charakteristischen Symptome der Krankheit vorzukommen.

Das C-Virus gehört ohne Zweifel zu den Erregern, die das

Syndrom der akuten abakteriellen Meningitis hervorrufen können, und man sollte in Zukunft nicht unterlassen, diese Ätiologie durch serologische Untersuchungen nachzuprüfen. Nicht selten besteht neben der Infektion mit dem C-Virus noch eine andere, zum Beispiel mit dem Poliomyelitisvirus oder dem Parotitisvirus. Deshalb ist eine gewisse Vorsicht bei der Beurteilung des C-Virus als ätiologischen Faktors bei Erkrankungen des Zentralnervensystems geboten.

9. Andere, ätiologisch noch unbekannte Virus-Enzephalomeningitiden

Auch wenn man alle heute zur Verfügung stehenden diagnostischen Mittel anwendet, um die Ätiologie einer Enzephalitis oder Meningitis festzustellen, bleibt doch eine gewisse Anzahl der Fälle unaufgeklärt. Da die Annahme am nächsten zu liegen scheint, dass Virusinfektionen im Spiele sind, muss man auch annehmen, dass es noch andere Viruskrankheiten gibt, die neutrop sind und obligate Enzephalomeningitiden mit dem Syndrom der akuten abakteriellen Meningitis verursachen können. Die Zukunft wird lehren, ob diese Auffassung richtig ist oder nicht.

II. Leptospirosen

Leptospirenerkrankungen sind während und nach dem letzten Weltkriege in steigender Anzahl in verschiedenen Teilen Europas und auch in aussereuropäischen Ländern beobachtet worden. Ähnlich wie bei den letzterwähnten nordamerikanischen Enzephalitiden spielen auch bei den Leptospirosen domestizierte und wilde Tiere eine führende Rolle als Erreger-Reservoir. Die Leptospirosen haben während des letzten Jahrzehnts sehr starkes Interesse unter den Klinikern, Epidemiologen und Bakteriologen geweckt, teils wegen der Zunahme entdeckter Erkrankungen bei Menschen, teils infolge der bakteriologischen und serologischen Möglichkeiten, die man jetzt besitzt, um sie zu diagnostizieren.

Man hat eine Reihe Leptospiren als Erreger von Krankheiten bei Menschen nachgewiesen, und wahrscheinlich wird die Zahl der Arten noch steigen. Obwohl die charakteristischen Krankheitserscheinungen dieser Leptospirosen bei Menschen nicht vom

Zentralnervensystem herrühren, kann es doch vorkommen, dass der Erreger Enzephalitis oder Meningitis hervorruft. Ganz wie bei anderen Enzephalomeningitiden ist die klinische Vermutungsdiagnose an das gleichzeitige Auftreten typischer Fälle der fraglichen Krankheit gebunden. Neben voll ausgeprägten klinischen Krankheitsbildern finden sich in derselben Anhäufung auch atypische Fälle, die wie eine reine Enzephalomeningitis verlaufen.

Die ätiologische Diagnose der sporadischen Fälle von Leptospiren-Enzephalomeningitiden kann nur mit Hilfe bakteriologischer und serologischer Untersuchung gestellt werden. Die Leptospiren können während der ersten Krankheitswoche aus dem Blut und Liquor in der zweiten aus dem Urin gezüchtet werden. Spezifische Antikörper sind von der zweiten Woche an nachweisbar. Die Leptospiren können in feuchtem Milieu lange leben. Sie dringen durch Hautverletzungen oder durch die intakten Schleimhäute in den Körper ein. Direkte Übertragung von Mensch auf Mensch spielt eine unbedeutende Rolle. Die Inkubationszeit beträgt etwa ein bis zwei Wochen.

Die Leptospiren-Enzephalitiden kommen, wie die Leptospirosen überhaupt, besonders bei Menschen vor, die beruflich mit der Tierspezies zu tun haben, welche von der fraglichen Leptospirenkrankheit befallen ist, oder bei Personen, die in der Nähe dieser Tiere wohnen oder dort ihre Beschäftigung haben.

1. Die Weilsche Krankheit. (*Leptospira icterogenes*.)

Die Weilsche Krankheit ist die zuerst entdeckte Leptospirose bei Menschen. Das Erreger-Reservoir sind Ratten. Schon lange hat man bei der Weilschen Krankheit Enzephalomeningitiden beobachtet und beschrieben, auch ohne die für die Krankheit typischen Erscheinungen (Icterus). Die Zugehörigkeit der letzteren Fälle zur Weilschen Krankheit ergab sich aus dem epidemiologischen Zusammenhang oder aus bakteriologisch-serologischen Untersuchungen. In Ausnahmefällen kann die Leptospirose auch Krankheitsbilder hervorrufen, die zum Syndrom der akuten abakteriellen Meningitis gehören.

2. Schweinehüterkrankheit. (*Leptospira pomona*.)

Eine andere Leptospirenkrankheit, die unter verschiedenen Namen schon seit längerer Zeit bekannt ist, die man aber erst nach dem Kriege als Leptospirenkrankheit erkannt hat, ist die sogenannte Schweinehüterkrankheit, die von der *Leptospira pomona* verursacht wird. Auch diese Krankheit verläuft sehr oft mit einer Meningoenzephalitis, bisweilen unter dem Bilde der akuten abakteriellen Meningitis. Der Krankheitsverlauf ist zweigipflig: zuerst eine grippeähnliche Erkrankung mit hohem Fieber und Muskelschmerzen, die drei bis fünf Tage oder länger dauert und mit meningitischen Symptomen sowie makulopapulösem Exanthem einhergehen kann, kurz danach ein zweiter Krankheitszustand mit Fieber und ausgesprochenen Meningitis-symptomen, der nur einige Tage anhält und in Heilung übergeht. Die Spinalflüssigkeit enthält, auch in Fällen ohne Meningitis-erscheinungen, eine lymphozytäre oder, besonders im Beginn, eine leukozytäre Pleozytose.

3. Die *Canicola*-Krankheit. (*Leptospira canicola*.)

Eine dritte Form von Leptospirenkrankheiten, die mit Meningoenzephalitis einhergehen kann, ist die bei Menschen seltene *Canicola*-Krankheit, welche bei Hunden vorkommt und von diesen auf Menschen übergehen kann. Mehrere Fälle von *Canicola*-Krankheit, die dem Syndrom der akuten abakteriellen Meningitis entsprechen, sind beschrieben worden.

4. Andere Leptospirosen, die Enzephalomeningitis erzeugen können

Noch eine Leptospirose ist bei Menschen identifiziert worden: das Feldfieber, durch *Leptospira grippotyphosa* verursacht. Die Krankheitssymptome sind die einer Grippe. Meningoenzephalitis kann vorkommen. Das Leptospiren-Reservoir ist die Feldmaus.

III. Andere Typen von enzephalitiserzeugenden Erregern

Nur ein paar Worte möchte ich den Enzephalomeningitiden widmen, die zur dritten Hauptgruppe des angegebenen Schemas gehören. Diese in der Regel sporadisch auftretenden Krankheiten

verlaufen mit charakteristischen Symptomen von Erkrankung des Zentralnervensystems, die im allgemeinen nicht denen der Enzephalomeningitis gleichen entsprechen, von der hier die Rede ist. Hierher gehören die Toxoplasmose (1) und die Torulose (2).

SABIN hat zwei Fälle von Toxoplasmaenzephalitis bei sieben- bis achtjährigen Kindern beschrieben, die mit lymphozytärer Spinalflüssigkeit und Toxoplasma im Liquor verlief. Eines der beiden Kinder starb, das andere genas.

VOYLES, MOSBERG und ARNOLD haben ein Krankheitsbild vom Typus der akuten abakteriellen Meningitis beobachtet, das durch Torulosis hervorgerufen worden war. Die Torula konnte aus dem Liquor auf Sabourauds Substrat gezüchtet werden.

Ob auch die Rickettsienkrankheiten (3) unter dem Bilde der Enzephalomeningitis verlaufen können, ist mir nicht bekannt, ebensowenig, ob noch andere als die hier erwähnten Erreger (4) eine Rolle spielen können.

Zusammenfassung

Zusammenfassend möchte ich folgendes sagen. Während der 27 Jahre, die nach der Prägung des Begriffes akute aseptische oder abakterielle Meningitis vergangen sind, ist eine Reihe von spezifischen Infektionen isoliert und erkannt worden, die dieses Syndrom erzeugen können. Diese Infektionen gehören in ätiologischer Hinsicht zu zwei Hauptgruppen von Erregern: Virus und Leptospiren. Dazu kommt eine dritte Gruppe von verschiedenen Agenzien, die nur in seltenen Ausnahmefällen ein ähnliches Krankheitsbild hervorrufen können wie Toxoplasmose, Torulose etc.

Die Viruskrankheiten des Zentralnervensystems sind entweder als seltene sekundäre Komplikationen anderer, nicht neutroper Viruskrankheiten (Masern, Röteln, Wasserpocken) aufzufassen, oder sie sind Ausdruck der Affinität desselben Virus zum Zentralnervensystem. Diese letztgenannten Enzephalomeningitiden treten als frequente Erscheinung bei der Virusinfektion auf. Sie kommen entweder als fakultative oder als obligate Erkrankung vor.

Die Viruskrankheiten mit fakultativer Enzephalomeningitis können ohne Enzephalitis verlaufen und sind durch andere charakteristische Symptome gekennzeichnet. Andererseits können sie ohne diese charakteristischen Züge, nur mit Erscheinungen seitens des Zentralnervensystems auftreten und gleichen dann ganz dem Syndrom der akuten abakteriellen Meningitis. Hierher gehören die Poliomyelitis, die Parotitis epidemica, die Herpesinfektionen und die infektiöse Mononukleose.

Die Viruskrankheiten mit obligater Enzephalomeningitis kommen, soweit bekannt, nur als Enzephalomeningitiden vor. Hierher gehören die Enzephalitis lethargica, die akute lymphozytäre Choriomeningitis, die St. Louis-Enzephalitis, die westliche und östliche Pferdeenzephalitisinfektion, die japanische B-Enzephalitis, die russische Wald-Frühling-Enzephalitis und die Coxsackie Virusenzephalitis.

Mit Ausnahme der lethargischen Enzephalitis können diese obligaten Enzephalomeningitiden sowie die Parotitis epidemica, die Herpesinfektionen und die Poliomyelitis durch Virus- oder Antikörpernachweis ätiologisch aufgeheilt werden. Alle diese Enzephalitiden können, mehr oder weniger frequent, das Syndrom der akuten abakteriellen Meningitis zeigen.

Die zweite Hauptgruppe von enzephalitisierenden Erregern bilden die Leptospiren. Hier sind es besonders die durch die *Leptospira icterogenes* und *pomona*, selten die durch die *Leptospira canicola* hervorgerufenen Krankheiten, die mit Enzephalomeningitis verlaufen können. Die für diese Erkrankungen charakteristischen Züge können fehlen und die Leptospirose sich nur als eine fieberige Enzephalomeningitis darstellen, die nicht selten dem Syndrom der akuten abakteriellen Meningitis entspricht. Die Ätiologie dieser Leptospirenkrankheiten wird während der Krankheit durch Erregernachweis und nach ihr durch Antikörpernachweis festgestellt.

Für die heutigen europäischen Verhältnisse spielen die aparyalytische Poliomyelitis, die Parotitis epidemica, die Herpesinfektionen, die akute lymphozytäre Choriomeningitis, die C-Viruskrankheiten und die Leptospirosen die Hauptrolle bei der Entstehung von Krankheitsbildern vom Typus der akuten abakteriellen Meningitis oder Enzephalomeningitis. Alle diese Infektionen muss man in Zukunft bei der ätiologischen Diagnose berücksichtigen.

Auch bei Zuhilfenahme aller diagnostischen Mittel, die jetzt zu Gebote stehen, bleibt jedoch ein gewisser Teil der Fälle von akuter abakterieller Meningitis ätiologisch unaufgeklärt. Man muss daher annehmen, dass es ausser den hier erwähnten noch andere spezifische Infektionen gibt, die dieses Syndrom hervorrufen können.

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PROCEEDINGS OF PEDIATRIC SOCIETIES

Proceedings of the Norwegian Pediatric Society

Meeting, February 23, 1951.

L. E. Carlgren (Stockholm): **Diagnosis of congenital malformations of the heart in children.**

A short review of the most important methods of investigation. The author stresses the importance of the unipolar leads in the electrocardiogram (the Wilson leads) for the diagnosis of hypertrophy of the heart. The fluoroscopic examination is an important part of the roentgen examination and must be performed both in the right and the oblique projection. Some anomalies can be accurately diagnosed by these examinations, but in many cases cardiac catheterization or angiocardiology is necessary for the exact diagnosis. The risks with these later methods are small and as regards the catheterisation of the heart, the risks are practically negligible.

S. Eek: **The roentgenologic appearances in coarctation of the aorta.**

The embryonic development of the great vessels is shortly reviewed. The haemodynamic and the pathologic-anatomic relations of the infantile and the adult forms of coarctation are described and then the roentgenologic findings. The enlargement of the left ventricle is mostly located to the outflow tract, whereby the aortic ostium gets displaced to the right. This again displaces the pulmonary ostium to the right so that the pulmonary artery forms the contour in A-P-position and the superior left contour of the heart seems long and often concave. The poststenotic dilatation of the aorta descendens regularly makes an impression in the shadow of the contrastfilled oesophagus. This impression gives (checked in 14 operated cases) good information of the exact position of the stenosis, its length and the extent of the poststenotic dilatation. In the above mentioned material was a boy, who, at $2\frac{3}{4}$ years of age, had already notching of the ribs. Another patient had notching of the ribs only on the right side, because the left subclavian artery originated from the stenosis. Another patient had notching of the ribs only on the left side. Here the right subclavian artery originated from the aorta as the last vessel on the aortic arch, went behind the oesophagus and

made an impression in the posterior wall of the contrastfilled oesophagus. Thoracic aortography is seldom necessary. It may, however, be of value in a few cases where the usual roentgenologic examination and planigraphy does not give the diagnosis.

Meeting, April 6, 1951.

G. Henriksen: Epilepsy and electroencephalography.

Will be published in Tidsskrift for Den Norske Lægeforening, Oslo.

M. Skatvedt: The drugs of the Tridione-group in the treatment of epilepsy. From the Children Hospital, Rikshospitalet, Oslo.

The drugs used have been Tridione, Paradione and the Norwegian drugs Afidion and Epinyl (5,5-Diphenyloxazolidine-2,4-dione and 3-Ethyl-5,5-dimethyloxazolidine-2,4-dione.). 19 patients in all have been treated. 16 had typical petit mal attacks and 13 of these had an E. E. G. showing a 3-per-second complex of spike and waves. In 3 patients no E. E. G. was taken. 2 patients had grave disorders of conduct but not seizures. Their E. E. G. showed 3-per-second complexes. 1 patient had myoclonic jerks, athetosis and abnormal E. E. G.

The observation time is short, from 3 months to 2 years. None of the patients have shown signs of agranulocytosis, one had a temporary eosinophilia and none had photophobia.

In 4 patients treatment had to be stopped because of skin eruptions, one patient having an almost fatal bullous dermatitis. One patient became ataxic after the use of Tridione in 1½ year. 3 patients showed marked behaviour disorders after small doses of Tridione or Paradione; they became restless, unruly and very noisy. In 2 of them the treatment had to be stopped. 4 patients suffering from petit mal became free from seizures. One patient, 9 years old, had an 3-per-second complex and a criminal past, seemed to be without inhibitions and was strongly suspected of being the cause of at least one fire. After 3 months of treatment with Tridione he was quiet and orderly. 3 patients were improved, but not free from seizures. They are still under treatment. 2 patients were free from seizures a short time in the hospital, but relapsed after they came home in spite of continued treatment. 2 patients had stopped taking the drugs after the discharge from the hospital. One patient we have not seen later, he was improved when in the hospital, but not free from his seizures. 6 patients showed no improvement in spite of large doses of Tridione and Paradione.

Meeting, May 25, 1951.

L. Wennevold: Cerebral palsies.

L. Bernstein: **Speech treatment in children with cerebral palsies.**

Discussion: Ugland, Rinvik, Wergeland, Salomonsen.

Bj. Andersen: **Permanent intravenous infusion in infants.**

Will be published later in Journal of The Oslo City Hospitals.

J. Ugland: **A case of acrodermatitis enteropathica, in a patient with fibrosis of the pancreas, treated with cortone.**

Will be published later in Acta Paediatrica.

Proceedings of the Section for Pediatrics and School Hygiene of the Swedish Medical Society

Meeting, March 9, 1951.

R. Zetterström: **The Effect of Vitamin D on the Mineral Metabolism of Bone.**

In cases of pronounced deficiency of vitamin D, a precipitation of mineral salts will occur in certain parts of bones. This precipitation takes place in areas where the osteoblasts have completely differentiated (cp. WILTON). Other parts of the osteogenetic tissue remain uncalcified, on account of a decreased cellular activity. Considering that calcification may occur in certain areas, a deficient calcification in a rickety bone may not be due exclusively to a lowered concentration of phosphate or calcium in the plasma. An explanation has also, partly, to be looked for in changes in the metabolism of the osteogenetic tissue. In vitro tests on isolated enzyme systems have shown that the phosphorylated, water-soluble vitamin D may affect the activity of the cells by activating the bone phosphatase and increasing the intensity of the oxidation processes.

G. Laurell: **Nosocomical Staphylococcal Infections In Children.**

This investigation took place at Sachsska Barnsjukhuset (Children's Hospital) during the years 1947—49. The special purpose of the bacteriological diagnoses has been to ascertain the presence of any staphylococcus aureus in the respiratory tract in children in hospital, as well as in the staff of the particular departments. Attention has, in particular, been paid to the possibility of aerial transmission of staphylococci. In the study of suspect cases of aureus infections, recourse has also been had to serodiagnosis (antistaphylolysin titrations), phage typing and determinations of the resistance to various antibiotics.

B. Werner: Demonstration of an Infusion Apparatus, tried at Sachsska Barnsjukhuset.

The apparatus has been constructed by Dr. B. Gustavsson, Assistant Professor at the Institute of Histology in Lund.

Will be published later in Svenska Läkartidningen.

B. Zetterström: Electroretinograms (ERG) in Children During the First Year of Life.

The origination and development of the ERG during the first year of life has been studied in 38 children. At birth, the ERG is missing, or consists of a faint elevation of the base line. In the course of the first year of life, a distinct rise in the b-potential occurs. The type of the ERG in an infant differs from that of adults. At an age of one year, it will, however, practically conform, in type and size, to that of adults.

P. Köhlin: Acute Pancreatitis in Children.

An account is given of five cases in Sweden of this rare disease. Excepting such benign forms as appear in parotitis and abdominal trauma, the course of the disease is usually fatal. Sudden abdominal pains, vomiting fits, sometimes diarrhea, a distended abdomen that feels tender when deeply palpated with few signs of rigidity, and, further, shock are the most significant symptoms, apart from the characteristic elevated distasic figures in urine and serum. In children, the disease is much less frequently connected with diseases in the bile ducts than in adults. Apparently, gastro-intestinal infections constitute a more important factor. Therapy aiming at overcoming the shocked condition has proved particularly effective. A summary of 27 cases described in the literature was given.

Meeting, May 2, 1951.

Professor G. Fanconi (Zürich): Chronic disturbances in the calcium balance.

Elias Bengtsson: The anamnesis in myocarditis in children.

An extensive and homogeneous material has been collected at the out-patients' department of the Epidemic Hospital. About 3 000 cases of scarlatina and, in addition, some cases of angina tonsillaris have been examined in a uniform manner. All the patients have been given a formulated series of questions, with a view to ascertaining any deterioration that may have occurred in their general condition, as well as any appearance of specific cardiac symptoms. 91 cases of myocarditis were noted. 3 per cent of the uncomplicated cases had general symptoms,

such as weariness and malaise. Other symptoms were rare. Contrariwise, the cases of myocarditis disclosed general symptoms in more than two thirds of the cases. In addition, they showed, in from one third to one half of the cases, symptoms of deteriorated physical condition, breathlessness, difficulty in walking uphill, fatigue at games, loss of stamina, etc. In one fifth of the cases, more specific symptoms, such as precordial pains, were noticed. Patients who, during or after the hospitalization, had developed infections in the upper air-passages or other complications (altogether 395 cases) revealed the same symptoms of weariness and deterioration in the general condition as the cases of myocarditis, though in less than 10 per cent of their total. Throughout, a statistically significant difference was obtained, as against cases complicated with myocarditis.

N. Svanborg: A case of nephrosis in a child less than 3½ years of age.

The patient is a boy, now 10 years old. Since 1947, he has had a nephrosis with a low amount of seralbumin, oedema, increased amount of serum lipid cholesterol and an electrophoretic diagram typical of nephrosis. Blood pressure and renal function were constantly normal.

During the first months of 1947, the patient was treated with aminosal per os and plasma transfusions. A certain remission was noticed, lasting for a few months. When his condition again grew worse, an inoculation of measles was tried. However, it only resulted in a subclinical manifestation of morbilli, without any definite improvement in the nephrosis. Now, also the plasma transfusions failed to produce any remission but, after a few weeks without treatment, a possibly spontaneous improvement set in. From the Spring of 1949, the patient was in a bad condition and two ACTH courses could bring about only spells of abatement of about 2 weeks. In March 1950, the patient developed a coli pleurisy and, simultaneously with a loss of weight, the oedema disappeared for three months. During that period, a course of DOCA and ascorbic acid was administered. 11 days after the suspension of the DOCA, a slight oedema reappeared. After a few weeks, it vanished. Since then (August, 1950) the patient has been free from oedema and felt healthy and strong. Control examination in April 1951 showed normal general condition, good renal function, practically normal amounts of lipids and albumin in the serum and almost quite normal electrophoretic diagrams. Thus, the patient is completely untroubled by his disease, though still showing about 2 per mille of albumin in the urine.

G. Falk: Inoculation and poliomyelitis.

An account is given of 420 cases of poliomyelitis, including 294 with pareses, all treated during 1949—51, at the Epidemic Hospital in Stock-

holm. Only 6 of the paretic cases had been vaccinated or given serum injections within one month before the onset. One of these patients had been inoculated against diphtheria. None of them had been given pertussis vaccine. In no instance had any definite connection between the localization of the paresis and the site of the inoculation been found.

J. Lindahl: Clinical aspects of Coxsackie-virus infections.

A brief summary is given of the discovery and occurrence of the Coxsackie- or C-virus. Pharyngeal, faecal and urinary samples from 607 patients, treated at the Epidemic Hospital of Stockholm for various diseases, chiefly acute infectious diseases, have been examined with regard to the occurrence of C-virus. In 14 instances, Coxsackie-virus has been isolated. The virus was detected in 12 faecal and 3 pharyngeal samples, as well as in one sample of urine. In one case of laboratory infection, no C-virus proved ascertainable, but during convalescence the patient developed such a marked rise in neutralizing antibodies as to suggest the likelihood that the patient has been subject to a C-virus infection. Neither the subjective symptoms nor the objective findings have revealed any characteristic features of the new virus disease. Nine of the fifteen cases displayed a typical clinical syndrome of poliomyelitis. Four of these had paresis. In faecal samples from two paretic cases, Coxsackie-virus, as well as poliomyelitic virus, were found. In one case, the electrocardiogram showed signs of myocarditis. In three instances, dysrhythmia was electroencephalographically registered. In one case, muscle biopsy was performed.

Sven Gard and Torsten Johnsson: Different types of Coxsackie-virus.

The types of the 16 strains of Coxsackie-virus, isolated at the Institute of Virology of the Karolinska Institute, from patients who, in most instances, have been treated at the Epidemic Hospital in Stockholm, have been determined by neutralization tests. 6 American strains, defined by Dalldorf, belonging to Group A, and one B-strain have been used as standards of comparison. At the preliminary investigation, the 16 Swedish strains have been reduced to 8 distinct types of Group A. 4 American types are identical with 4 Swedish ones. When the patients are classified according to the particular types, no specific symptomatology traits could be ascertained.

DISCUSSION. — *O. Gabinus:*

An account was given of an investigation regarding the occurrence of Coxsackie-virus in epidemic myalgia (Bornholm disease). The investigations were performed at the Institute of Virology of the Karolinska Institute, Stockholm (Head: Professor Sven Gard). The C-virus investiga-

tions were carried out on hospitalized cases of epidemic myalgia (as well as, in some few instances, on cases of serous meningitis without any signs of epidemic myalgia, though an epidemiologic connection with epidemic myalgia had been found). All cases occurred in the Autumn of 1950 at Jönköping-Huskvarna. During that time, no poliomyelitis with paresis was noted in that district. The investigations are still proceeding, but the following preliminary results may be of interest. In 7 of the 21 cases of epidemic myalgia, or serous meningitis of the same nature, C-virus was found. In one instance, C-virus was ascertained in urine, pharyngeal secretion and faeces, in another case in pharyngeal secretion and faeces, and in the remaining 5 cases in faeces. The neutralization test has, so far, been concluded in but one case. There, a marked rise in the titre was obtained during the progress of the disease. In a small control material (13 cases), consisting of virus encephalitis, mumps meningitis and pneumonia, no C-virus has been found in any case. *This preliminary investigation result suggests the possibility of a certain connection between C-virus and epidemic myalgia. The laboratory infections, described by Shaw, Melnick & Curnen, favour the same view.*

Meeting at Uppsala, May 25, 1951.

L. Söderhjelm: Case of Renal Acidosis.

A typical case of renal acidosis (tubular insufficiency without glomerular insufficiency) in a girl 10 years old. Rapid progression with acidosis and pronounced hypokaliemia before death. The post-mortem showed disseminated nephrocalcinosis with destruction of the papillae.

Å. Gyllenswärd: W. P. W. — Syndrome.

L. Tivenius: A Case of Morbus Hand-Schüller-Christian.

A girl aged 3, previously healthy, had suffered from polyuria and polydipsia for the last 6 months. X-ray of the skeleton showed multiple destruction of the bones, especially of the temporal bone and the cranial base. A sample of decayed bone taken from the scapula confirmed the diagnosis. The patient has no exophthalmus, however. The patient has reacted positively to hypadrin.

B. Vahlquist: Gammaglobulin in Pediatric Practice.

To be published in Svenska Läkartidningen.

L. Söderhjelm: Some Observations on Muscular Diseases in Children.

To be published in Acta Pædiatrica.

B. Hagberg: The Anemia of Infection.

The appearance and degree of anemia during infection depends primarily on the type and intensity of the infectious disease. An individual disposition probably also plays some role. Certainly, the pathogenesis is of a complex nature. Factors of special importance are: a diversion of the body's iron from the site of hemoglobin production, a depression of erythrocyte formation in the bone marrow and an increased destruction of red cells in certain infections, e.g. septicemias. Recent investigations with isotopes have given valuable information about the mechanism of production of the anemia, especially iron metabolism.

The author has studied the iron-binding capacity of blood serum in infected children with and without anemia. The preliminary results support the idea that the successive decline of iron-binding capacity during infection does not cause anemia of infection. To demonstrate the increased destruction of erythrocytes in septic diseases, the survival time of transfused red blood cells was determined according to the method of Ashby. In one case, a girl 5 months old, with a resistant hemophilus influenza meningitis and accompanying anemia of infection the survival time was only 39 days, or considerably shorter than the normal period of 120 days. The cause of this type of hemolysis is so far unknown. Probably there are hemolysing substances of bacterial origin in plasma and may be also a general inferiority of the red blood cells.

S. Sjölin: Aniline Pencils and Gastric Lavage.

A gastric lavage was carried out on a boy, aged 21 months, one hour after he had been found sucking an aniline pencil. The amount of water used was so large, that water intoxication with hyponatremia and generalized convulsions ensued. After a large quantity of urine had been passed, the boy recovered quickly.

The problem was whether the symptoms were due to toxicity of the aniline pencils. In Sweden, these pencils have hitherto been regarded as toxic, maybe because of the attribute "aniline". The dye in the aniline pencils, however, does not consist of the toxic aniline, but of para-rosaniline-derivatives (methyl violet, crystal violet, gentian violet). The toxicity of these para-rosaniline stains is low. Sometimes they may irritate the gastric mucosa and cause nausea, vomiting and diarrhoea, but no other toxic reactions have been noticed. Gentian violet may be given without inconvenience to adults in a dose of 0.2 grams daily for periods of 10 days. Aniline pencil sticks, however, may be injurious to the conjunctiva and the cornea, and deposited subcutaneously they cause slow-healing wounds. In 1930, Ilkoff also presented a case in which the swallowing of a 3 cm long aniline pencil stick was responsible for a later gastric ulcer, but no intoxication followed. In one case only

intoxication and death has been attributed to the sucking of an aniline pencil (Nord. Med. 29, 243, 1946), but one may question whether this case cannot have been a water intoxication too.

To conclude, the sucking of aniline pencils need hardly be regarded as dangerous as has been customary in Sweden. Furthermore, it is essential to remember, that gastric lavage is a procedure not free from risk.

(To be published in detail in Nordisk Medicin.)

J. A. Bök: Genetics and Hospital Pediatrics.

Genetics applied to medicine offers an important complementary method of analyzing the etiology of a large number of diseases and defects. Apart from this basic research, the data now available have also some practical consequences for the socio-medical field. The pediatrician is often concerned with genetic diseases and defects which raise practical problems for the families concerned. Anxious parents want to know the risk of further children being affected. Affected persons may raise the question of the advisability of parenthood or genetic advice might be requested in cases of adoption.

Table 1.

Some genetic diseases and defects due to single recessive gene differences. A risk figure of 25 per cent for sibs of the affected patient can be used safely if both parents are unaffected (which is the rule).

Disease or defect	Approximate frequency among newborn or morbidity risk
Albinism.....	1:10 000—1:20 000
Phenylketonuria.....	1:50 000
Friedreich's ataxia.....	1:50 000
Genetic deaf-mutism.....	1:5 000—1:10 000
Fibrosis of the pancreas.....	1:1 000—1:10 000
Juvenile amaurotic idiocy.....	1:40 000
Infantile amaurotic idiocy.....	1:250 000—1:3 000 000
Achromatopsia.....	1:300 000
Ichtyosis congenita gravis (lethal).....	1:300 000—1:1 000 000
Retinitis pigmentosa ¹	1:20 000
Microcephaly (true microcephaly).....	1:50 000
Glycogenosis.....	1:200 000

¹ The common type: there are also sex-linked recessive and dominant types.

Table 2.

Empiric risk figures for a number of genetic¹ or possibly² genetic diseases and defects.

Disease or defect	Approx. frequency among newborn or morb.-risk	Risk for sibs. Parents unaffected	Risk for sibs. One parent affected	Risk for children of one affected parent
Anencephaly ²	1:1 000	1 %	—	—
Chondrodystrophy ¹	1:10 000	0.01 %	50 %	50 %
Congenital clubfoot ¹	1:1 000	3 %	10 %	—
Congenital luxation of the hip ¹	1:1 500	5 %	10—15 %	—
Malformations of the CNS (unspecified) ²	1:200	3 %	—	—
Convulsive disorders (grand mal) ²	1:300	2—4 %	—	3—6 %
Diabetes mellitus, appearing before the age of 50 ¹	1:200	15—20 %	—	10—15 %
Harelip or harelip combined with cleft palate ¹	1:1 000	4 %	14 %	2 %
Cleft palate alone ¹	1:2 500	2—12 %	17 %	7 %
Imbecility or feeble-mindedness (unspecified) ¹	1:100	13—18 %	30—40 %	30 %
Mongoloid idiocy ²	1:700	1—4 %	—	—
Congenital cataract with idiocy ¹	1:50 000	15 %	—	—
Microphthalmus or anophthalmus with idiocy ¹	1:100 000	10 %	—	—
Strabismus ¹	1:50	10 %	17 %	—
Pyloric stenosis ¹	1:250	5 %	—	—

Such advice should be very useful, provided that they give objective information based on reliable data. They should not be misunderstood as part of so called eugenic programs for which sufficient scientific data are still lacking.

For a few conditions caused by simple recessive, dominant or sexlinked genes with complete penetrance the risk may be theoretically calculated on the basis of mendelian segregation. In most cases, however, the genes concerned have a variable or incomplete penetrance, or the participation of genetic factors may be questioned. Still, it will often be possible for the specialist in medical genetics to offer a reasonably well founded prognosis after a study of the family pattern.

Furthermore compound empiric risk figures are now available for a number of conditions of genetic or supposedly genetic origin. Such

figures just express the statistical chance and are not bound to any particular theory of the etiology of the condition.

Table 1 gives a list of conditions which are recognized as due to single recessive gene differences and table 2, a list of conditions for which reasonably accurate empiric risk figures are available.

As the number of genetic diseases and defects which the pediatrician may have to deal with at one time or another is almost unlimited, the selection for these tables must necessarily be somewhat arbitrary. However, such conditions have been selected which appear with a known frequency in the population and for which the risk figures are backed up by a sufficient body of data. Furthermore, the frequency figures are those which at our present level of knowledge best fit the conditions in Sweden. Differences may occur in comparison with other geographical regions and some of the tabulated disorders may be entirely absent.

A. Frantzell, B. Hagberg, and L. Söderhjelm: Soft Tissue Radiography and Urinary Excretion of Creatine in Infants with Arthrogryposis Multiplex Congenita and Werdnig-Hoffmann's Infantile Muscular Atrophy.

BOOK REVIEW

J. JOCHIMS: Praxis der antibiotischen Behandlung im Kindesalter. Beihefte zum Archiv für Kinderheilkunde, 27. Heft, Stuttgart 1951.

This book is a practical guide to the use of antibiotics in pediatrics. The author reviews the literature and adds his own experiences. He stresses the importance of an etiological diagnosis. The necessary bacteriological specimens should (at least in all severe cases) be taken before starting treatment. It is often necessary to make a determination of the bacteria resistance in vitro to different antibiotics. A knowledge of the drug concentration in the infected organ is also necessary for the selection of the proper drug. In this connection the author might have mentioned the value of bacteriological control during treatment with antibiotics, especially if any complication occur.

The author warns against the uncritical use of antibiotics and stresses the side-effects: toxic and allergic reactions, effect on the normal bacterial floras and the lowering of immunity (and of the development of resistant strains).

Each antibiotic drug (terramycin included) is briefly described with special regard to its clinical use.

Two thirds of the book comprises indications for antibiotic therapy in different diseases. The literature is reviewed adequately and the advice given is clear and practical.

Rutger Lagercrantz, Stockholm.

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